Seraseq™
HIV-1 Reference Material

Package Insert

PLEASE NOTE:
THESE REAGENTS MUST NOT BE SUBSTITUTED FOR THE MANDATORY POSITIVE AND NEGATIVE CONTROL REAGENTS PROVIDED WITH MANUFACTURED TEST KITS.

NAME AND INTENDED USE
The Seraseq™ HIV-1 Reference Materials are high titer viral isolates (Table 1), intended for use with targeted Next Generation Sequencing assays that determine subtype, identify drug resistance mutations or assign viral tropism. The Seraseq HIV-1 Reference Materials, which can be ordered individually, are intended for use by diagnostics manufacturers, researchers, and clinical laboratories to develop, evaluate, or troubleshoot HIV-1 assays such as next-generation sequencing (NGS). *For Research Use Only. Not for use in diagnostic procedures.*

SUMMARY
A well-designed quality control program can provide added confidence in the reliability of results obtained for unknown specimens. The use of independent controls and reference materials may provide valuable information concerning laboratory proficiency and kit lot variation that may affect assay sensitivity[1].

PRINCIPLES OF THE PROCEDURE
Seraseq HIV-1 Reference Materials contain live HIV-1 virus cultured in stimulated human peripheral blood mononuclear cells. Eight (8) of the reference material strains were originally derived from the NED panel, an international HIV-1 Subtype Reference and Standard Panel[2]. The virus is diluted in defibrinated human plasma. The reference materials should follow the same workflow as unknown samples and require viral nucleic acid extraction prior to use in Next Generation Sequencing (NGS) assays. The materials are provided at approximately 1.0E+06 viral copies/mL.

The Seraseq HIV-1 Reference Materials were used by the HIV Forum (a public-private consortium addressing issues of NGS applied to viral pathogens) in their NGS Proficiency Panel project. Therefore, the sequence of these isolates was verified across multiple laboratories and multiple sequencing platforms.

REAGENTS
Items No. 0740-0001 through 0740-0012. 1 vial, 1 mL per vial, 1.0E+06 viral copies/mL concentration.

WARNINGS AND PRECAUTIONS
For Research Use Only. Not for use in diagnostic procedures.
CAUTION: Handle Seraseq HIV-1 Reference Material and all materials derived from human blood products as though they are capable of transmitting infectious agents. Seraseq HIV-1 Reference Materials are formulated in defibrinated human plasma, tested and found negative for common bloodborne pathogens (negative for the presence of antibody to HIV1/2, antibody to HCV, antibody to HBc, antibody to HTLV I/II, HIV RNA, HCV RNA, HBV DNA and HBsAg).

Safety Precautions
Use Centers for Disease Control and Prevention (CDC) recommended universal precautions for handling reference materials and human specimens[3]. Do not pipette by mouth; do not smoke, eat, or drink in areas where specimens are being handled. Clean any spillage by immediately wiping up with 0.5% sodium hypochlorite solution. Dispose of all specimens and materials used in testing as though they contain infectious agents.

Handling Precautions
Avoid contamination of the product when opening and closing the vials.

STORAGE INSTRUCTIONS
Store Seraseq HIV-1 Reference Material frozen at -70°C or colder. Once thawed and opened, an individual vial of Seraseq HIV-1 Reference Material should not be reused.

INDICATIONS OF REAGENT INSTABILITY OR DETERIORATION
Seraseq HIV-1 Reference Material is cultured HIV-1 virus suspended in defibrinated human plasma. It will appear as a yellow to amber liquid. Alterations in this appearance or visible microbial growth may indicate instability or deterioration of the product and vials should be discarded.

PROCEDURE
Materials Provided
Seraseq HIV-1 Reference Material is whole, intact HIV-1 virus diluted in defibrinated human plasma. One (1) mL is provided per tube and the concentration is approximately 1.0E+06 viral copies/mL as determined by a TaqMan based, real time PCR assay.

Materials Required but not Provided
Refer to instructions supplied by manufacturers of the test kits to be used.

Instructions for Use
Allow the vial to come to room temperature before use. Mix by vortexing to ensure a homogeneous suspension. Seraseq HIV-1 Reference Material should be added to a test run using the same procedure provided by the manufacturer for unknown specimens. Seraseq HIV-1 Reference Material must go through an extraction process prior to library preparation and NGS sequencing. The Reference Materials should go through the nucleic acid extraction, target selection and library preparation in parallel with the test specimens. Refer to your usual assay procedures in order to determine the amount of material to use.

Quality Control
Seraseq HIV-1 Reference Material does not have assigned values for the drug resistant mutations or the variant allele frequencies. However, the product has been sequenced by multiple laboratories using multiple sequencing platforms (as listed in Table 1) and bioinformatics pipelines. There are many reasons why assays may observe deviation from the representative data which may or may not be of significance. It is therefore recommended that each laboratory qualify the use of Seraseq HIV-1 Reference Material with each assay system prior to its routine use.

INTERPRETATION OF RESULTS
Levels of reactivity of Seraseq HIV-1 Reference Material may vary with different types of tests and different test kit lots. Since the reference material does not have an assigned value, the laboratory must establish a range for each lot of Seraseq HIV-1 Reference Material. When results for the product are outside of the established acceptance range, it may indicate unsatisfactory test performance. Possible sources of error include: deterioration of test kit reagents, operator error, faulty performance of equipment, contamination of reagents or change in bioinformatics pipeline parameters.

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LIMITATIONS OF THE PROCEDURE

Seraseq HIV-1 Reference Materials MUST NOT BE SUBSTITUTED FOR THE CONTROL REAGENTS PROVIDED WITH MANUFACTURED TEST KITS.

TEST PROCEDURES and *INTERPRETATION OF RESULTS* provided by manufacturers of test kits must be followed closely. Deviations from procedures recommended by test kit manufacturers may produce unreliable results. Seraseq HIV-1 Reference Materials are not calibrators and should not be used for assay calibration. Adverse shipping and storage conditions or use of outdated product may produce erroneous results.

EXPECTED RESULTS

Specific detection of variants and variant allele frequencies will vary among different assays, different procedures, different lot numbers, and different laboratories. Each laboratory should establish its own range of acceptable values. For example, the acceptable range might include all values within 2 standard deviations of the mean of 20 data points obtained in 20 runs over a period of 20 days[4]. Table 1 lists key characteristics for the viral strains that are present in the product.

SPECIFIC PERFORMANCE CHARACTERISTICS

Seraseq HIV-1 Reference Materials have been designed for use with NGS sequencing procedures for the purposes of assessing assay performance. Seraseq HIV-1 Reference Materials do not have assigned values. Procedures for implementing a quality assurance program and monitoring test performance on a routine basis must be established by each individual laboratory.

REFERENCES

1. Green IV GA, Carey RN, Westgard JO, Carten T, Shablesky LA, Achord D, Page E and Le AV. Quality control for qualitative assays: quantitative QC procedures designed to assure analytical quality required for an ELISA for hepatitis B surface antigen. Clin. Chem. 43:9 1618-1621, 1997.

2. Huang, DD, Giesler, TA, and Bremer, JW. Sequence characterization of the protease and partial reverse transcriptase proteins of the NED panel, an international HIV type 1 subtype reference and standards panel. AIDS Res Hum Retroviruses. 2003 Apr;19(4):321-8.

3. Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee, 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings.

4. Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline-Second Edition. NCCLS document C24-A2, 1999.

5. Johnson VA, Calvez V, Günthard HF, Paredes R, Pillay D, Shafer RW, Wensing AM, and Richman DD. Update of the Drug Resistance Mutations in HIV-1: March 2013. Topics in Antiviral Medicine 21:1 6-14.

Table 1: Isolates and Panel information

#	Item number	Isolate ID	Sub type	Country	Tropism	Drug Resistance Mutations (>5%)[1]	NGS Platform Confirmed
1	0740-0001	BK132	B	Thailand	X4	None	Illumina MiSeq and Ion PGM™
2	0740-0002	93/US/144	B	USA	R5	None	Illumina MiSeq and Ion PGM™
3	0740-0003	CM237	B	Thailand	X4	None	Illumina MiSeq and Ion PGM™
4	0740-0004	US1	B	USA	R5	None	Illumina MiSeq and Ion PGM™
5	0740-0005	93/US/143	B	USA	X4	None	Illumina MiSeq and Ion PGM™
6	0740-0006	93/US/141	B	USA	R5	PR: L10I RT: T215Y, K219Q	Illumina MiSeq and Ion PGM™
7	0740-0007	I-2496	CRF02_AG	Ghana	R5	None	Illumina MiSeq and Ion PGM™
8	0740-0008	CM235	CRF01_AE	Thailand	R5	None	Illumina MiSeq and Ion PGM™
9	0740-0009	7388	B	USA	X4	RT:41L / 67N 210W / 215Y /184V / 69D / 44D / 118I	Illumina MiSeq and Ion PGM™
10	0740-0010	7384	B	USA	X4	RT: 41L / 67N / 70R / 215F /219E /69N	Illumina MiSeq and Ion PGM™
11	0740-0011	2529	B	USA	X4	RT: 74V, 41L, 106A, and 215Y	Illumina MiSeq and Ion PGM™
12	0740-0012	2808	B	USA	DM/X4	PR:V82F / L97V	Illumina MiSeq and Ion PGM™

[1] Drug resistance mutations are as defined in Johnson VA et al[5]. Other mutations may be present, but their association with drug resistance is not well established and they are not listed here.

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