Adding a Diagnostic Claim to HIV Prognostic Assays: Why Not NAT?

2016 HIV Diagnostics Conference
March 22, 2016

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Purpose of this Talk

• Understand the regulatory issues associated with adding a diagnostic claim to an HIV viral load assay
• Identify likely requirements to get that claim
• Understand the logic/reasoning behind those requirements
• Recommended next steps
Issue

- HIV viral load assays detect HIV RNA
- The function of a diagnostic NAT is to detect HIV
- Why, then, can’t viral load assays be used for diagnosis?
Dissecting the Issue:
What Most People See
INTENDED USE: What is detected in what sample?

SPECIMEN  →  HIV NAT  →  HIV RNA? [HOW MUCH?]
Dissecting the Issue: What FDA Sees
INTENDED USE: What is detected in what sample?

SPECIMEN → HIV NAT → HIV RNA? [HOW MUCH?]

From whom? → Then what?

INDICATIONS FOR USE: For what purpose?

The bottom line...

ALL CLAIMS MUST BE SUPPORTED BY DATA
HIV Viral Load Assay Intended Use Statement

[NAME OF TEST] is an in vitro RT-PCR assay for the quantitation of HIV-1 on the [NAME OF INSTRUMENT] in human plasma from HIV-1 infected individuals over the range of 40 to 10,000,000 copies/mL. The assay is intended for use in conjunction with clinical presentation and other laboratory markers for disease prognosis and for use as an aid in assessing viral response to antiretroviral treatment as measured by changes in plasma HIV-1 RNA levels. This assay is not intended to be used as a donor screening test for HIV-1 or as a diagnostic test to confirm the presence of HIV-1 infection.
Data to Support Viral Load Assay Claims (1)

• Stability (specimen, test kit, shipping)
• Limit of Detection (LoD)
• Linear range
• Reproducibility
• Potentially interfering substances, including anti-retrovirals
Data to Support Viral Load Assay Claims (2)

• Specificity
  – \( \geq 500 \) blood donors
  – Unrelated medical conditions
  – Cross-reactivity with other microorganisms

• HIV subtypes and groups

• Linearity

• Method correlation
What would be needed to support a dx claim?

It depends...

...on what the claim is.

In other words...
What's The Use?

INDICATIONS FOR USE!
The APTIMA® HIV-1 RNA Qualitative Assay is an in vitro nucleic acid assay system for the detection of human immunodeficiency virus (HIV-1) in human plasma. It is intended for use as an aid in the diagnosis of HIV-1 infection, including acute or primary infection. Presence of HIV-1 RNA in the plasma of patients without antibodies to HIV-1 is indicative of acute or primary HIV-1 infection.

The APTIMA HIV-1 RNA Qualitative Assay may also be used as an additional test, when it is reactive, to confirm HIV-1 infection in an individual whose specimen is repeatedly reactive for HIV-1 antibodies. This assay is not intended for use in screening blood or plasma donors.
HIV Diagnostic NAT Intended Use Statement

The APTIMA® HIV-1 RNA Qualitative Assay is an in vitro nucleic acid assay system for the detection of human immunodeficiency virus (HIV-1) in human plasma. It is intended for use as an aid in the diagnosis of HIV-1 infection, including acute or primary infection. Presence of HIV-1 RNA in the plasma of patients without antibodies to HIV-1 is indicative of acute or primary HIV-1 infection.

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Diagnostic Assay Intended Use?

HIV-1/2 antigen/antibody combination immunoassay

(+)

HIV-1/2 antibody differentiation immunoassay

(-)

Negative for HIV-1 and HIV-2 antibodies and p24 Ag

HIV-1 (+) HIV-2 (-)
HIV-1 antibodies detected

HIV-1 (-) HIV-2 (+)
HIV-2 antibodies detected

HIV-1 (+) HIV-2 (+)
HIV antibodies detected

HIV-1 (-) or indeterminate

HIV-2 (-)

HIV-1 NAT

(+)

HIV-1 NAT (+)
Acute HIV-1 infection

(-)

HIV-1 NAT (-)
Negative for HIV-1

(+ or -) indicates reactive or nonreactive test result
NAT: nucleic acid test

Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. CDC, June 2014
What studies could carry over from a VL NAT to a dx claim?

• Stability (specimen, test kit, shipping)
• Reproducibility
• Analytical sensitivity
• Potentially interfering substances (but likely not concerned about anti-retrovirals)
• Unrelated medical conditions
• Cross-reactivity with other microorganisms
• Detection of HIV subtypes and groups
Additional Studies for a Dx Claim

- Seroconversion panels
  - Compare to EIA and Western blot to support acute infection detection claim

- CBER HIV-1 RNA panel
  - 0, 100, 1,000, 25,000, and 250,000 cp/mL (100% detection expected)

- Clinical specificity studies
  - $\geq$ 3,500 low risk (blood donors ok – compare to licensed HIV-1 NAT)

- Clinical sensitivity studies
  - $\geq$ 1,000 known HIV-1 RNA-positives, distributed among different disease stages
  - $\geq$ 300 high risk for HIV infection
Additional studies: Supplemental claim

• Include specimens that are:
  – 4\textsuperscript{th} generation test repeatedly reactive
  – HIV-1/2 differentiation assay HIV-1 negative or indeterminate/HIV-2 negative

• Discuss with FDA for more specifics
Next Steps

• Decide what indications for use are most appropriate/useful for an HIV diagnostic NAT
• Use the Pre-Submission process to get feedback from FDA on study design proposals (including size of study)
• Show that the benefits outweigh the risks if need to deviate from FDA expectations