A Signal-to-Cutoff Ratio in the Abbott Architect HIV Ag/Ab Combo Assay That Predicts Subsequent Confirmation of HIV-1 Infection in a Low-Prevalence Setting

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A rapid diagnosis is considered important in HIV care. In 138,911 testing episodes with the Abbott Architect HIV Ag/Ab Combo assay (3,705 reactive samples), a signal-to-cutoff ratio of >151.17 had a positive predictive value of 100% and a sensitivity of 67.4% for the detection of subsequently confirmed HIV infection. We suggest that results higher than this signal-to-cutoff ratio threshold may be reported to clinicians before the completion of confirmatory testing.

HIV testing algorithms aim to minimize the time to confirmation of the diagnosis with maximum sensitivity and specificity. The Abbott Architect HIV Ag/Ab Combo assay (Abbott Combo; Abbott Laboratories, Abbott Park, IL, USA) is a chemiluminescent microparticle immunoassay that simultaneously detects HIV-1 p24 antigen (Ag), HIV-1 gp41 antibody (Ab), and HIV-2 gp36 Ab. The magnitude of the chemiluminescent signal is reported as a signal-to-cutoff (S/CO) ratio. It is a commonly used screening test, as it has a sensitivity and specificity of >99% and >98%, respectively (1–3).

Confirmatory testing is typically undertaken with highly specific Western blot (WB) analysis or, more recently in some countries, including the United States, an HIV-1–HIV-2 differentiation immunoassay that proceeds to a qualitative nucleic acid test for any discordant case (4).

We hypothesized that the positive predictive value (PPV) of the Abbott Combo assay for HIV-1 infection increases with the S/CO ratio and that test results higher than a specific S/CO ratio can be rapidly communicated to clinicians without awaiting supplemental test results. Such a threshold may also inform the use of single testing algorithms in resource-poor settings. As the PPV is dependent on the prevalence of infection in the population sampled, the objective of the study was to identify an S/CO ratio with a 100% PPV for HIV-1 infection in Australia, which has a low HIV prevalence of 0.15% (5).

Other studies with small samples have suggested a relationship between the S/CO ratio in HIV Ag/Ab assays and confirmed HIV infection or the HIV viral load (VL) (1, 6–8). As the somewhat time-consuming HIV WB test is the currently approved confirmatory test in Australia, we assessed the positive predictive value of the Abbott Combo assay in this low-prevalence population.

We retrospectively analyzed all Abbott Combo testing episodes from a large serology diagnostic laboratory in Sydney, Australia, between March 2006 and March 2014. All serum samples were tested with the Abbott Combo assay, and reactive results were tested in duplicate after centrifugation at 10,000 × g for 10 min. If at least one of the repeat tests was reactive, three supplemental tests were performed: a p24 Ag enzyme immunoassay (EIA) with confirmatory neutralization (Vironostika HIV-1 Ag [bioMérieux, Marcy l'Etoile, France] or Genscreen HIV-1 Ag [Bio-Rad, CA,

USA]), a WB test (MP Diagnostics HIV-1/2 Blot 2.2; MP Bio-medicals, CA, USA), and an HIV-1 Ab particle agglutination assay (Serodia-HIV; Fujirebio, Tokyo, Japan). HIV VL testing was performed with the Cobas Amplicor HIV-1 monitor test (Roche, Basel, Switzerland), the Versant HIV 3.0 (bDNA) assay (Siemens, Bavaria, Germany), or the Cobas AmpliPrep/Cobas TaqMan HIV-1 test 2.0 (Roche) and was undertaken at the discretion of the treating clinician.

The following supplemental test combinations led to a reactive result being classified as true positive: an initial positive WB test or a positive WB test within 6 months ($n = 2,072$); a negative or indeterminate WB test and at least two positive results in the p24 Ag assay, the HIV Ab assay, or the HIV VL test ($n = 320$); and a negative or indeterminate WB test, a positive p24 Ag or HIV Ab assay, and no HIV VL available ($n = 150$). Previous studies support the specificity of this classification, and further details are given in Table S1 in the supplemental material (9–18). The remaining testing episode results were pooled as non-true positives.

The test episodes were then randomly allocated to two equally sized samples, a train sample and a test sample (see Table S1 in the supplemental material for details). The train sample was used to identify the S/CO ratio above which all reactive serum samples were considered true positives. Finally, the PPV and sensitivity of this S/CO ratio for a true-positive result in the test sample were calculated.

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FIG 1 Cumulative frequency distribution of the S/CO ratios of true and non-true positive Abbott Architect HIV Ag/Ab Combo assay testing episodes.

The local Human Research Ethics Committee approved the research.

A total of 138,911 Abbott Combo testing episodes were analyzed, of which 3,705 were repeatedly reactive and 2,542 were deemed to be true-positive results. The cumulative frequency distributions of the S/CO ratios of true and non-true positives in the total sample are shown in Fig. 1. Patient age, proportion of males, and S/CO distribution were not different in the test and train samples (see Table S2 in the supplemental material). Patients with non-true-positive Abbott Combo tests were younger and more likely to be female and had significantly lower mean S/CO ratios than patients with true-positive results.

The highest S/CO ratio in non-true-positive episodes in the train sample was 151.17. When applied to the test sample as the lower discriminatory value, this produced a PPV of 100% with a sensitivity of 67.4% for confirmed HIV-1 infection, meaning that more than two-thirds of all subsequently confirmed reactive Abbott Combo tests were correctly identified. Table 1 shows the PPVs and sensitivities at selected S/CO ratios. The sensitivity may be higher than that reported here due to misclassification of some true positives as non-true positives. A secondary analysis using only the first sample for each individual did not alter the results (data not shown). Since the PPV is directly proportional to the prevalence, it can be hypothesized that a lower S/CO ratio than that reported here may be discriminatory with a similar PPV in higher-prevalence settings.

Potential limitations of this study include the retrospective data collection, the short (2-week) window for inclusion of VL test results in the assessment of each episode, and the HIV-1 subtype B predominance in this population (78% of new diagnoses in 2013 and rare HIV-2 cases), which may limit generalizability (5). Before application of this approach, the threshold S/CO ratio should be reassessed to control for factors such as local isolate variation and host differences.

TABLE 1 Performances of selected S/CO^a ratios in the Abbott Architect HIV Ag/Ab Combo assay when used as thresholds for a true-positive result in the test sample

S/CO ratio	Positive predictive value for a true-positive result (%)	Sensitivity for a true-positive result (%)
>151.17	100	67.4
>100	99.7	73.8
>50	99.0	80.6

^a S/CO, signal-to-cutoff.

To our knowledge, this study presents the largest analysis to date of the PPV of the Abbott Combo S/CO ratio. Knowledge of the S/CO ratio allows for the test result of the Abbott Combo to be used in clinical decision making. We suggest that a result with a sufficiently high S/CO ratio be reported immediately and accompanied by a statement that although a false-positive result is extremely unlikely, confirmatory testing will be undertaken. The clinician may then deliver a positive test result to the patient or direct investigation and treatment of an acute presentation without having to wait for confirmatory testing.

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