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Reproducibility of the cobas CMV test (cobas CMV) and clinical concordance with the Cobas Ampliprep/Cobas TaqMan CMV test (CAP/CTM CMV)

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Background: The cobas CMV is a new, automated, high-throughput assay for use on the cobas 6800 and cobas 8800 instrument systems that quantifies CMV DNA in plasma samples. It can be run in mixed batches with other assays due to a uniform assay design. We evaluated the reproducibility of cobas CMV and concordance of results between this assay and CAP/CTM CMV among clinical plasma specimens.

Material/methods: Reproducibility of cobas CMV was determined by testing EDTA-plasma spiked with cultured CMV virus (Merlin) at concentrations of 0, 100, 1,800, 7,200 and $5x10^6$ IU/mL across multiple days, reagent kit lots, and operators at 3 clinical laboratories. Concordance of results between cobas CMV and CAP/CTM CMV was evaluated using longitudinal plasma samples from solid organ transplant (SOT; n=1913 samples from 107 subjects) and hematopoietic stem cell transplant (HSCT; n=1367 samples from 257 subjects) recipients who participated in clinical trials for prophylaxis against CMV infection and disease. Clinical concordance at representative CMV viral load threshold levels (e.g., 1,800 IU/mL) and for decision to stop antiviral therapy (based on two sequential results of <137 IU/mL) was determined. For assay method comparison analysis, initial viremic plasma sample from each SOT or HSCT subject and additional 68 cross-sectional clinical plasma samples plus 219 contrived samples were used.

Results: cobas CMV showed high reproducibility with an SD of <0.11 $\log_{10}$ IU/mL and an overall detectable difference of <0.31 $\log_{10}$ IU/mL for all panel members, with most variability found in the

lowest concentration member, attributable to within-run random error. Among SOT recipients, cobas CMV and CAP/CTM CMV were concordant at a 1,800 IU/mL decision point, with 96.7% overall agreement. The decision to stop antiviral therapy would be >86.2% concordant, with cobas CMV usually resulting in a longer duration of therapy. Among HSCT recipients, both assays were concordant at a 1800 IU/mL decision point with 99.3% overall agreement. The decision to stop therapy would be 100% concordant although this was only evaluable in 26 subjects. The two assays were highly concordant with no significant bias among the contrived samples made from cultured virus. When results for clinical plasma samples were compared, cobas CMV yielded higher viral loads than CAP/CTM CMV with a bias of 0.25 $\log_{10}$ IU/mL and 0.16 $\log_{10}$ IU/mL in SOT and HSCT recipients, respectively.

Conclusions: The new cobas CMV is highly reproducible and is calibrated to the WHO international standard. Possibly due to limitations in the commutability of the WHO standard, cobas CMV may yield higher CMV DNA values than CAP/CTM CMV in clinical plasma samples, but both assays generated concordant results necessary for clinical decision making. Note: cobas CMV is not available in all markets and its performance characteristics are subject to FDA approval.