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Validation of an enhanced sensitivity Trofile™ HIV-1 co-receptor tropism assay for selecting patients for therapy with entry inhibitors targeting CCR5

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Background

Trofile is a clinically validated HIV-1 co-receptor tropism assay for selecting patients for therapy with entry inhibitors targeting CCR5. Trofile determines whether a patient virus population is CCR5 (R5), CXCR4 (X4) or dual (R5/X4)/mixed (D/M)-tropic and has demonstrated utility in clinical trials of CCR5 antagonists including maraviroc and vicriviroc. Existing studies suggest that detection of patients with lower levels of CXCR4-using variants may further optimize patient selection for CCR5 antagonist therapy. We therefore developed an enhanced sensitivity Trofile assay with improved ability to detect low levels of CXCR4-using virus.

Methods

Experiments were conducted to validate the performance of the enhanced Trofile assay for patient management applications in compliance with CAP and CLIA regulations. The tropism of viral isolate and patient-derived HIV-1 envelopes (Envs) were evaluated to assess assay accuracy. Assay precision and reproducibility were assessed by replicate testing and minor variant sensitivity was determined using mixtures of patient-derived R5 and X4 env clones.

Summary of results

Trofile enhancements increased detection sensitivity for X4 Envs by approximately 30-fold on average. X4 clones present at 0.3% were detected in 100% of assays. The lower limit of X4 detection was env clone pair (patient) dependent and ranged from 0.003–0.3%. Enhanced Trofile accurately determined the tropism of 46 patient samples and isolates representing multiple subtypes, including 14/18 clonally analyzed patient samples with X4 variants below the detection limit of the original Trofile assay. Intra-assay precision (100%) and inter-assay reproducibility (99%) were demonstrated by concordant results for 135/135 and 228/230 pair-wise comparisons of R5, X4 and DM Envs and repeat testing of 46 patient Env populations, respectively.

Conclusion

In conclusion, these validation experiments demonstrate that the enhanced Trofile assay has improved sensitivity to detect CXCR4-use in env clone mixtures and patient env populations compared to the original Trofile assay, while assay accuracy, precision and reproducibility are maintained. This increases the utility of the Trofile assay for selecting patients for CCR5 antagonist therapy.