

Oral presentation

O115 Importance of detecting minority variants in the clinical management of HIV

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from Ninth International Congress on Drug Therapy in HIV Infection
Glasgow, UK. 9–13 November 2008

Published: 10 November 2008

Journal of the International AIDS Society 2008, 11(Suppl 1):O5 doi:10.1186/1758-2652-11-S1-O5

This abstract is available from: <http://www.jiasociety.org/content/11/S1/O5>

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HIV-1 drug resistance is an important cause of antiretroviral failure. Although standard genotypic and phenotypic tests can detect drug resistance in many cases, both are limited in their capacity to detect variants present as minority members of the viral population, particularly at levels below 5–10%. Recently, several studies have shown that drug-resistant minority variants present in the population prior to initiation of antiretroviral therapy substantially increase the risk of treatment failure. These minority variants may represent persistence of transmitted drug-resistant viruses or may represent mutants that have arisen de novo during the course of infection. Two studies from our laboratory used different approaches to the detection of minority variants. In the first study, allele-specific real-time PCR was used to detect and quantify presence of minority variants carrying non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations in baseline plasma samples from subjects enrolled into AIDS Clinical Trials Group (ACTG) protocol A5095, which compared the efficacy of three- and four-drug efavirenz-based regimens. Presence of Y181C mutations even at levels below 1% was associated with a nearly 2.5-fold greater risk of virological failure. In a second study, ultra-deep pyrosequencing was used to characterize the diversity of V3 loop sequences from HIV-1 env present within infected persons, and to track the dynamic evolution of the quasispecies in response to treatment with the investigational CCR5 antagonist vicriviroc (VCRV). V3 loop forms associated with subsequent virologic failure, either through CXCR4 use or the emergence of high-level VCRV resistance, were present as minor variants at 0.8–2.8% of baseline samples. These studies, along with the work of other groups, illustrate the clinical significance of minority drug-resistant populations and the importance of developing and clinically validating novel technologies for their detection.