## S4.6

# CELLULAR RESISTANCE TO THE ANTIRETROVIRAL DRUGS

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It has been proposed that the declining efficiency of antiretroviral agents of HIV infection may also depend on cellular factors at their site of action. Two of them have been considered with particular emphasis. They are: i) the defective intracellular metabolism of nucleoside reverse transcriptase inhibitor (NRTI) in target cells and the altered uptake, and ii) efflux of NRTI and protease inhibitors (PIs) by cellular transporter molecules. Several studies have shown that: changes in the activities of various purine and pyrimidine biosynthetic enzymes may occur in lymphocytes of HIV-infected patients; HIV-infected patients on prolonged treatment with nucleoside analogs, such as AZT, show significantly decreased activity of TK compared to untreated HIV-infected persons; a inter-individual variability in plasma drug concentration and biosynthetic enzymes activity do exist; non nucleoside reverse transcriptase inhibitor (NNRTI), NRTI and PIs are substrates for the so-called multidrug membrane transporters and the overexpression of multidrug transporters significantly reduces the accumulation of PIs. As regard to the latter issue, it is known that the ATP-binding cassette transporter proteins such as the Pgp (MDR), and the newly discovered family of multidrug resistance-associated proteins (MRP1-8), promote the active extracellular efflux of a wide variety of therapeutic drugs and overexpression of some of them lowers intracellular concentration of PIs. In a very near future such mechanisms, also called "cellular drug-resistance", might be taken into account, together with other immunological, virological and behavioural factors, to explain the "drug failure" and/or the variability of response in HIV patients undergoing an antiretroviral treatment.