HIV drug resistance

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Since its availability in 1996, the use of highly active antiretroviral therapy (HAART) to treat HIV-infection has led to declines in AIDS morbidity and mortality rates. Unfortunately, these benefits can be compromised by the development of drug resistance mutations. The genetic and molecular basis of drug resistance is the enormous viral turnover coupled with an extremely high replication error rate.

To date twenty antiretroviral drugs have been approved for the treatment of HIV-1 infection: one nucleotide and seven nucleoside reverse transcriptase inhibitors (NRTIs), eight protease inhibitors (PIs), three nonnucleoside RT inhibitors (NNRTIs), and one fusion inhibitor. Resistance to antiretroviral drugs emerges when viral replication continues in the presence of selective drug pressure. For some drugs, such as the NRTI lamivudine and all NNRTIs, one point mutation is sufficient to induce high-level resistance, whereas other drugs like zidovudine and the PIs require the accumulation of multiple mutations to reach a high level of resistance. Thus, resistance to therapies consisting of combinations of different drugs develops in a gradual and stepwise manner.

Single mutations or mutational patterns can result in resistance to an entire drug class. A strain, which has emerged under the selective pressure of a specific drug, may be resistant not only to that drug, but also to other drugs from the same class that have never been applied. This phenomenon is referred to as cross-resistance. Cross-resistance affects almost all of the currently available drugs to varying degrees. Thus, resistance to one antiretroviral agent will affect the choice of other drugs from the same class.

Resistance to antiretroviral drugs can be measured using either genotypic or phenotypic assays. Genotypic assays detect mutations known to cause drug resistance, usually resulting in sequence data. Phenotypic assays are drug susceptibility assays in which the virus is cultured in the presence of serial dilutions of an inhibitory drug, providing the clinician with directly interpretable data.

Genotypic and phenotypic assays each have specific advantages and disadvantages. Because many laboratories are capable of performing automated DNA sequencing, genotypic testing is available from many more laboratories than is phenotyping. Genotyping is less complex, faster, and less expensive than phenotyping. But interpretation of genotypic results is challenging. Therefore, computational methods may assist in interpreting sequence information by predicting the phenotype from the genotype. Together with genetic barriers to drug combinations this approach provides extremely helpful information, especially in a patients salvage situation, where only few therapy options are left.