HIV Drug Resistance and Mother-to-Child Transmission of HIV

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• HIV • Antiretroviral resistance
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BASIC PRINCIPLES OF HIV DRUG RESISTANCE

Emergence of resistance to antiretroviral drugs can be quite virologically complex, yet has principles that can be simple to understand as a clinician.[1] HIV characteristically has a high rate of viral replication, which, coupled with continuous mutation and recombination events, enables it to develop resistance to any and all of the more than 20 antiretroviral drugs licensed for use.[1,2] Drugs that target the reverse-transcriptase enzyme include those characterized as nucleoside/nucleotide analogs because they are structurally related to endogenous nucleosides. Non-nucleoside reverse-transcriptase inhibitors are a broad group of drugs that also target reverse-transcriptase, but are structurally dissimilar to endogenous nucleosides and to each other. Protease inhibitors target the protease enzyme to interrupt assembly of the mature virion. Integrase inhibitors target the integrase enzyme to block integration of HIV into cellular DNA. Two drug classes target entry of HIV into the cell: fusion inhibitors and those that block the CCR5 receptor.

Retroviruses, such as HIV, do not have proofreading mechanisms when synthesizing new nucleic acid strands that results in frequent incorporation of unintended nucleotides during chain elongation.[1] This random substitution of nucleotides, coupled with the high turnover of HIV in vivo, enables virtually any and all genotypic mutations to occur. Some of these changes in genetic structure are associated with decreased susceptibility to antiretroviral drugs, with some single-point mutations conferring a high degree of resistance to certain drugs (eg, lamivudine, nevirapine, efavirenz); whereas, multiple mutations are needed to develop resistance to other drugs.

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There are two types of commercial HIV resistance tests available: genotypic tests and phenotypic tests. Both tests typically require a plasma HIV viral load greater than 1000 to 2000 copies/mL, and will only detect resistance that is present in greater than 10% to 20% of the circulating HIV in plasma. The phenotypic test is more expensive than the genotypic test. Genotypic resistance testing is the most common test performed and involves sequencing the nucleic acids that make up all 99 codons of the protease gene, the first approximately 335 codons of the reverse-transcriptase gene, and targeted portions of the integrase gene and envelope gene.[3] The sequence derived from the plasma of patients is compared with a consensus HIV-1, group M, subtype B virus (the most common strain in North America). Mutations are described by the letter indicating the consensus B wild-type amino acid followed by the amino acid number, followed by a letter indicating the amino acid mutant.[3] For example, T215Y (a common mutation associated with resistance to zidovudine) denotes a change at position 215 of the reverse-transcriptase gene from threonine (the consensus wild-type amino acid at that position) to tyrosine (the mutant amino acid). If there is a mixture of more than one amino acid detected at a position, each amino acid detected is denoted after the number. For example, T215T/Y indicates a detection of both the wild-type amino acid and the mutant. The phenotypic test measures the ability of HIV to replicate in the presence of a drug and reports results as a fold change in the inhibitory concentration compared with a sensitive strain of HIV. Phenotypic fold change may be reported in 2 manners: (1) as the fold change at which there is a reduction in antiviral activity and (2) the fold change above which there is essentially no drug activity.

Some drugs have a low genetic barrier to resistance because a single-point nucleic acid mutation can engender resistance.[3] For instance, a change of one nucleic acid in the reverse-transcriptase gene at amino acid 184 results in a change from methionine to valine (M184V), which confers high-level resistance to lamivudine and emtricitabine. For non-nucleoside reverse-transcriptase inhibitors, a single-point mutation at several positions of the reverse-transcriptase gene, most commonly 103 from lysine to asparagine (K103N) or 181 from tyrosine to cysteine (Y181C), are associated with high-level resistance to the first generation of non-nucleoside reverse-transcriptase inhibitors, nevirapine and efavirenz. The second generation, non-nucleoside reverse-transcriptase inhibitor, etravirine, maintains virologic activity in the presence of the K103N mutation; however, resistance to etravirine can be present if the Y181C mutation is also accompanied by additional mutations.

Resistance to protease inhibitors is complex with resistance-associated mutations documented at approximately 25% of the 99 amino acid positions.[1–3] Major mutations in the protease gene are those selected first in the presence of the drug (these may vary considerably by drug) and are typically the primary contact amino acid for that drug or are mutations that substantially reduce susceptibility to that drug. Minor mutations generally emerge over time and may improve the replicative capacity of viruses containing a major mutation. These mutations are sometimes referred to as compensatory mutations because they tend not to occur naturally in subtype B. However, some minor mutations in subtype B are also common polymorphisms in non-B subtypes. Protease inhibitors are typically coadministered with ritonavir to take advantage of its unique property to decrease the hepatic metabolism of many other drugs, including most protease inhibitors, resulting in what is commonly referred to as boosted protease inhibitors. Often, numerous mutations in the protease gene are necessary to impact virologic response to ritonavir-boosted regimens, and most boosted protease inhibitor-based regimens are said to have a high genetic barrier to resistance.[3]