

RESISTANCE TO NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NSRTIS) AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)

The first data suggesting correlation between the emergence of viral resistance and clinical progression was reported by Larder and colleagues¹ two years after AZT became available for clinical use.

AZT, ZDV: Mutations emerge in a characteristic sequence, with a first single base mutation usually appearing at codon 70. This appearance is temporary as it is typically replaced by a mutant at codon 215. This mutation is commonly followed by the appearance of single base mutations at codons 41, 67, and 219. The mutation at codon 70 may reappear with prolonged AZT treatment, as can a mutation at codon 210. These mutations (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) are known as *thymidine analogue mutations* (TAMs) because they confer cross resistance to d4T, another thymidine analogue, as well. Some experts favour the term *nucleoside-associated mutations* (NAMs) because some degree of cross-resistance has been documented between these mutations and all members of the NRTI class.

Mutations at codon 69 and 151 have also been associated with broad resistance to nearly all members of the NRTI class.

d4T: in addition to the TAMs and the mutations at codons 69 and 151 described above, mutations at codon 75 may be associated with resistance.

ddI: Resistance to ddI is associated with a mutation at codon 74 (L74V) as well as the TAMs and the mutations at codons 69 and 151. In addition, the K65R mutation may be associated with resistance.

3TC: *In vitro*, high-level resistance (500- to 1,000-fold) develops rapidly when the virus carries the single mutation M184V/I. This mutation is also observed *in vivo*. Furthermore, insertion at codon 69 is associated with resistance to 3TC.

ABC: *In vitro* selection for resistance to ABC has been associated with the TAMs and mutations at codon 184. Insertion mutations at codon 69 are also associated with resistance to ABC.

TDF: *In vitro* selection for reduced sensitivity to TDF has been associated with a mutation at codon 65 (K65R). *In vivo*, the mutation K65R has also been documented in patients failing TDF treatment. In addition, multiple TAMs and/or an insertion mutation at codon 69 can result in resistance to TDF.

As shown in *Table 18*, many mutations of the reverse transcriptase gene elicited by one ARV induce cross-resistance to other NRTIs.

¹Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science* 243:1731-1734; 1989.