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The bottleneck in AZT activati

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Nucleoside-based inhibitors of reverse transcriptase were the first drugs to be u the chemotherapy of AIDS. After entering cell, these substances are activated to th triphosphate form by cellular kinases, aft they are potent chain terminators for the viral DNA (ref. 1). The two main factors li their efficacy are probably interrelated. T the insufficient degree of reduction of vir at the commencement of treatment and t emergence of resistant variants of the vir reason for the relatively poor suppressior replication appears to be inefficient meta activation. Thus, for the most extensively drug, 3'-azido-3'-de-oxythymidine (AZT), whereas phosphorylation to the monopho is facile, the product is a very poor substr the next kinase in the cascade, thymidyla kinase[2,3]. Because of this, although high concentrations of the monophosphate cai reached in the cell, the achievable concer of the active triphosphate is several orde magnitude lower. Determination of the st of thymidylate kinase as a complex with A monophosphate (AZTMP) together with s on the kinetics of its phosphorylation hav led to a detailed understanding of the rea and consequences of the poor substrate properties.

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