

## Preface

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Inhibitors of nucleic acid biosynthesis have had a long and varied history as therapeutic agents. They have frequently provided the backbone of therapy in a wide variety of proliferative disorders ranging from infectious diseases to cancer. Because of the specialized and highly evolved synthetic chemistry in this area, the many analogs of nucleosides, nucleotides, and their biosynthetic precursors have found use as tools for basic research. It is not surprising that, upon discovery of the etiology of AIDS about twenty years ago—it is a syndrome associated with infection with a retrovirus—nucleoside analogs with potential antiviral activity against the virally encoded RNA-dependent DNA polymerase (reverse transcriptase) were among the first compounds to be screened.

*Reverse Transcriptase Inhibitors in HIV/AIDS Therapy* covers the discovery and development of this class of drugs and others inhibiting the same viral target from a therapeutic perspective. As the vanguard agents with efficacy in this disease, these nucleoside analogs were also the first to manifest the toxicities and resistance associated with chronic administration and inadequate single-agent potency. Nevertheless, they have retained their position as the backbone of therapy in the vast majority of newly treated and treatment-experienced patients. The discovery of several unrelated chemical classes of inhibitors, all binding to the same target, has meant for many patients that viral reverse transcriptase is the sole target for highly active drug combination therapy.

Human cells express many polymerases involved in essential functions. Therefore, there is every expectation that nonselective viral polymerase inhibitors would possess inescapable mechanism-based toxicities. The HIV reverse transcriptase, however, has no human counterpart, giving reason to believe that a wider safety margin might be achievable. This is still a challenging area of research.

The early chapters describe the role of reverse transcriptase in the viral life cycle and structural work that has led to a greater understanding of mechanism and resistance. The discovery and development of six nucleoside analogs are described in the next chapters. Among these are drugs representing milestones in treatment history, such as the benefit of combination therapy, as well as milestones in pharmaceutical manufacturing, such as coformulation. The inescapable topics of toxicities and resistance to this class are described in subsequent chapters.

The non-nucleoside reverse transcriptase inhibitors are described in a similar fashion in general terms, and two chapters discuss these agents with respect to pharmacokinetics and comparative clinical efficacy. New reverse transcriptase inhibitors in all classes in various stages of development are described in one chapter and the impact of the approved agents on treatment in general and on vertical transmission in the developing world are dealt with in the final chapters.

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