

HOSPITAL PHYSICIAN®

INFECTIOUS DISEASES BOARD REVIEW MANUAL

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The *Hospital Physician Infectious Diseases Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in infectious disease. Each quarterly manual reviews a topic essential to current practice in the subspecialty of infectious disease.

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Complications of Antiretroviral Therapy for HIV: Mechanisms of Action, NRTIs, and NNRTIs

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Complications of Antiretroviral Therapy for HIV: Mechanisms of Action, NRTIs, and NNRTIs

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INTRODUCTION

Antiretroviral therapy (ART) for HIV infection dates to 1987, when the nucleoside reverse transcriptase inhibitor (NRTI) azidothymidine (zidovudine) was found to improve survival in HIV-infected patients. Dramatic improvements in morbidity and mortality were noted with the addition of agents capable of inhibiting different targets in the HIV replication cycle, such as protease inhibitors (PIs, first approved in 1995), additional NRTIs, and non-nucleoside reverse transcriptase inhibitors (NNRTIs, first approved in 1996). The rate of AIDS deaths in the United States fell by 42% from 1996 to 1997, and admissions for HIV-related complications decreased 30% from 1995 to 1998.¹ In the United States, 20 agents have been approved by the Food and Drug Administration and are available at the time of this writing, including the March 2003 release of a drug with a novel mechanism of action, fusion inhibition (enfuvirtide, T-20). Concomitant with the success of antiretroviral agents in preserving the immune system and slowing disease progression, medication toxicity and complications of ART have become increasingly important. Antiretroviral choice should be determined by balancing side effect profiles, tolerability, and pill burden with potency of drug combinations and viral resistance patterns.

This 2-part series focuses on common and emerging complications of ART of which practitioners should be aware. Part 1 reviews antiretroviral mechanisms of action and discusses specific complications of NRTIs and NNRTIs in a case-based format. Part 2, which will be published in the next installment of the *Infectious Diseases Board Review Manual*, will address toxicities associated with PI therapy and the more recently approved antiretroviral agents.

ANTIRETROVIRAL MECHANISMS OF ACTION

HIV is a member of the retrovirus family, which stores its genetic information in the form of RNA. The initial step in viral replication utilizes an enzyme, reverse transcriptase, to produce a complementary DNA strand. Proviral DNA is then integrated into the host cell by viral integrase and serves as the genetic template for virus production. Polyprotein precursors are formed and cleaved into functional components of mature virions by viral protease. Virions are released and enter new host cells via fusion with the cell membrane, facilitated by a peptide complex, glycoprotein 41 and glycoprotein 120 (gp41/gp120), collectively referred to as glycoprotein 160 (gp160). Once inside the cell, the process repeats. Current ART is aimed at inhibiting 1 or more of these steps (**Figure**).

Four classes of antiretroviral agents are currently approved by the US Food and Drug Administration. NRTIs are analogues of the naturally occurring building blocks of DNA, the purine nucleosides, adenosine (A) and guanosine (G), and the pyrimidines, thymidine (T) and cytidine (C). In their phosphorylated state they are recognized by reverse transcriptase and incorporated into nascent viral DNA. The addition of cellular nucleosides is then prevented and further viral DNA synthesis cannot occur. In contrast, NNRTIs bind directly to reverse transcriptase, noncompetitively inhibiting enzymatic activity. They are structurally different from NRTIs and therefore have distinct toxicities, despite a common enzymatic target. PIs bind to the active site of viral protease and prevent processing of viral polyproteins into functional forms. Fusion inhibitors bind to gp41 and interfere with viral entry into target cells. The case studies that follow address potential causes of antiretroviral toxicity, with attention to known and suspected biological bases for these complications.