Antiretroviral Therapy

Current Drugs

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KEYWORDS

• HIV • Antiretroviral therapy • Nucleoside/nucleotide reverse transcriptase inhibitors
• Non-nucleoside reverse transcriptase inhibitors • Protease inhibitors
• Integrase strand transfer inhibitors • Fusion inhibitor • CCR5 antagonist

KEY POINTS

- To date, 28 antiretroviral drugs have been approved by the Food and Drug Administration.
- Effective combination antiretroviral therapy can durably suppress human immunodeficiency virus (HIV) viremia and has dramatically improved HIV-associated morbidity and mortality.
- For antiretroviral treatment-naïve patients, a combination regimen typically consists of 2 nucleoside reverse transcriptase inhibitors plus a third drug.
- Because of the increased number of options, the selection of an antiretroviral therapy regimen can be individualized, based on efficacy, adverse effects, comorbidity, dosing frequency, pill burden, potential for drug interactions, or drug resistance.
- Success and durable combination require strict adherence to long-term therapy.
- This article reviews the clinical pharmacology of the antiretroviral drugs commonly used in the United States.

INTRODUCTION

The 1980s saw the devastation of the newly emerging and deadly disease of acquired immunodeficiency syndrome (AIDS). The identification of the retrovirus, now known as human immunodeficiency virus (HIV), as the causative pathogen in the mid-1980s was the key milestone in the control of this disease. The discovery of the multistep replicative life cycle of HIV in human CD4+ T cells led to the identification of potential drug targets to halt or slow the replicative process (Fig. 1). This

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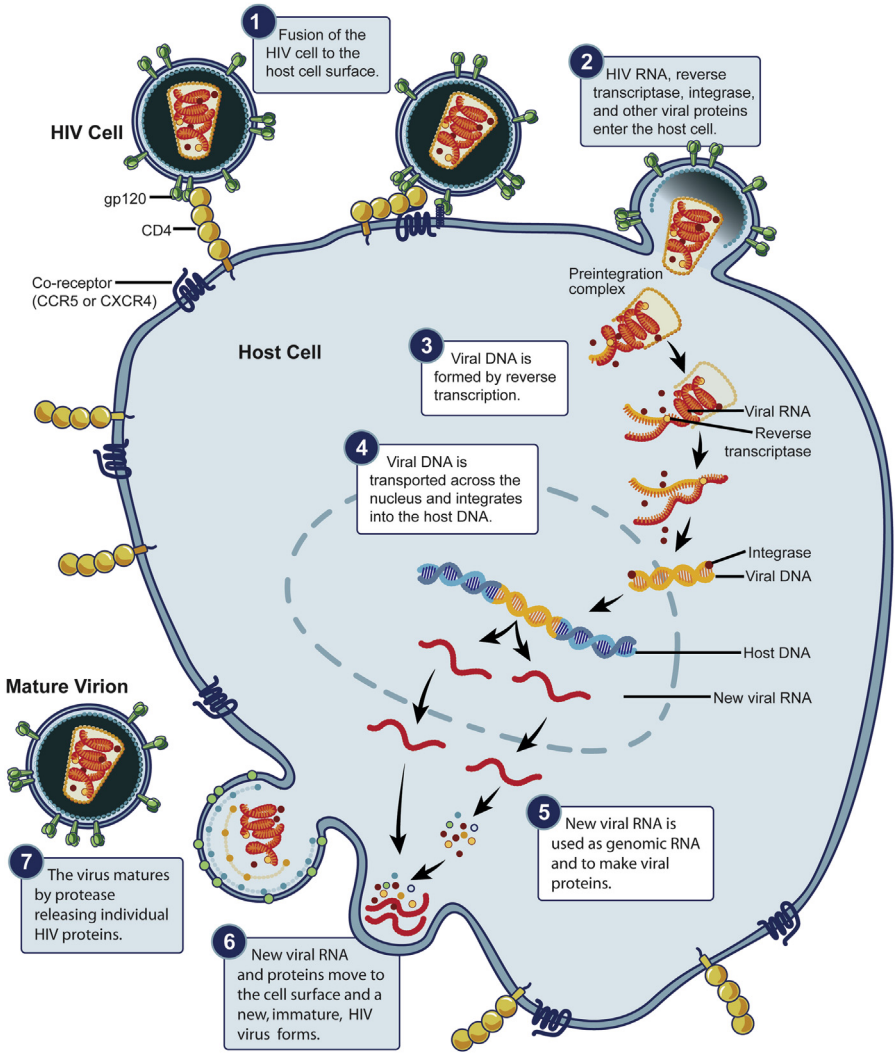

Fig. 1. HIV replicative life cycle. *Cell entry*: The first step of cell entry is the attachment of the HIV envelope glycoprotein gp120 onto human chemokine receptors (CCR5 or CXCR4) on the CD4 cell surface. After the initial attachment, the next step requires fusion of the viral and cell membranes, allowing the viral proteins to enter into the cytoplasm. *Reverse transcription*: After cell entry, as HIV is a retrovirus, the virus's RNA template transcribes into a double-stranded viral DNA in the presence of the enzyme reverse transcriptase. *Integration*: The viral double-stranded DNA produced after reverse transcription is then transported into the cellular nucleus. In the presence of the integrase enzyme, a multistep process allows the integration of viral DNA into host genome and ultimately formation of proviruses. *Formation of infectious virions by HIV proteases*: After successful integration of viral DNA into the host genome and formation of proviral proteins, the next step of the HIV-1 life cycle is the cleavage of these polyproteins and formation of infectious virions. The viral enzyme protease is the key element for this process. (*Adapted from* National Institutes of Allergy and Infectious Diseases. Available at: http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/pages/hivreplicationcycle.aspx. Accessed March 12, 2014; with permission.)