TREATMENT FOR (STD) HIV INFECTION

Prior to approval of zidovudine in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients rather than on inhibiting HIV itself.

This multi drug regimen is commonly referred to as highly active antiretroviral therapy, or HAART. There are five classes of antiretroviral drugs, each of which targets one of four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry inhibitors and the integrase inhibitors. The current recommendation for primary therapy is to administer two NRTIs with either a protease inhibitor or an NNRTI. Selection of the appropriate combination is based on

1) avoiding the use of two agents of the same nucleoside analog,

2) avoiding overlapping toxicities and genotypic and phenotypic characteristics of the Svirus,

3) patient factors such as disease symptoms and concurrent illnesses,

4) impact of drug interactions,

5) ease of adherence to a frequently complex administration regimen. The goals of therapy are to maximally and durably suppress viral load replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.

Drugs used to prevent HIV from replicating. [NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

NRTI Used to Treat HIV Infection

A. Overview of NRTIs

Mechanism of action: Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a3'-hydroxyl group. **Once they enter cells, they are phosphorylated by a variety of cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by virus reverse transcriptase**. Because the 3'-hydroxyl group is not present, a 3'-5'-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated. Drugs used to prevent HIV from replicating. [NRTI = nucleoside and nucleotide reverse

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VI. Nrtis Used to Treat HIV Infection

Pharmacokinetics: The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except *abacavir*, which is metabolized by alcohol dehydrogenase and glucuronyl transferase. Dosage adjustment is required when the creatinine clearance drops below 50 mL/min.

Adverse effects: Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues. As a general rule, the dideoxynucleosides, such as *zalcitabine, didanosine*, and *stavudine,* have a greater affinity forthe mitochondrial DNA polymerase, leading to such toxicities as peripheral neuropathy, pancreatitis, and lipoatrophy. When more than one NRTI is given, care is taken not to have overlapping toxicities. All the NRTIs have been associated with a potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis.

Drug interactions: Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for *zidovudine* and *tenofovir.*

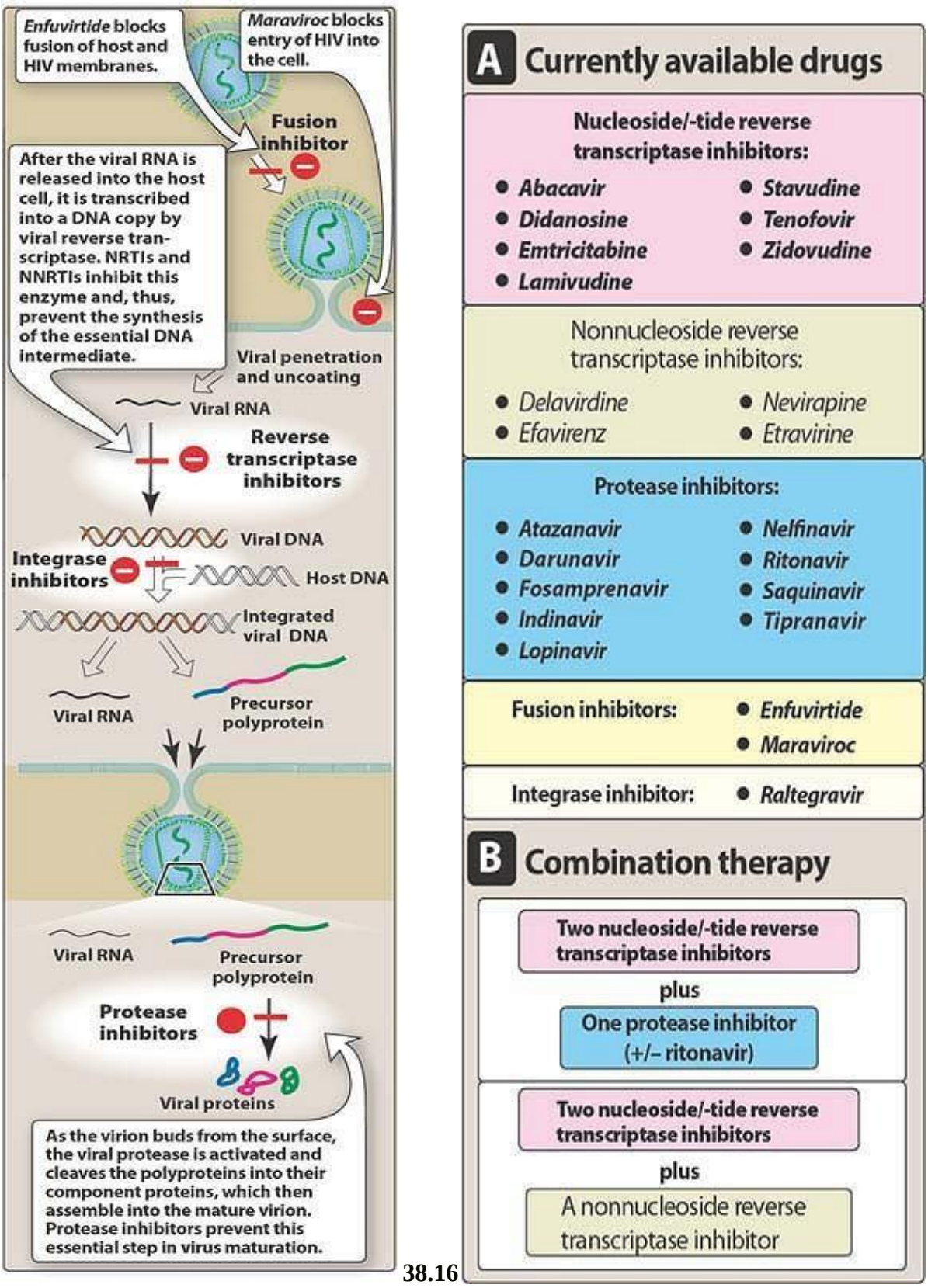
Resistance: NRTI resistance is well characterized, and the most common mutation is the mutation at viral codon which confers a high degree of resistance to *lamivudine* but, more importantly, restores sensitivity to zidovudine and tenofovir. Cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine and adenosine)

Highly active antiretroviral therapy (HAART).

B. Zidovudine (AZT)

Approved in 1987, the first agent available for treatment of HIV infection is the pyrimidine analog, 3'-azido- 3'-deoxythymidine (AZT). AZT has the generic name of zidovudine. AZT is approved for use in children and adults and to prevent prenatal

infection in pregnancy. It is also recommended for prophylaxis in individuals exposed to HIV infection. The drug is well absorbed after oral administration. If taken with food, peak levels may be lower, but the total amount of drug absorbed is not affected. Penetration across the blood-brain barrier is excellent, and the drug has a half-life of 1 hour. The intracellular half-life, however, is approximately 3 hours. Most of the AZT is glucuronylated by the liver and then excreted in the urine.



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