

Antiretrovirals: HIV and AIDS Drugs

Kyung Shika

Department of Medicine, Hanyang University, Seoul, South Korea, Email: shikakyu@gmail.com

The management of HIV/AIDS normally includes the use of multiple antiretroviral drugs in an attempt to control HIV infection. There are several classes of antiretroviral agents that act on different stages of the HIV life-cycle. The use of multiple drugs that act on different viral targets is known as highly active antiretroviral therapy (HAART). HAART decreases the patient's total burden of HIV, maintains function of the immune system, and prevents opportunistic infections that often lead to death.

Treatment has been so successful that in many parts of the world, HIV has become a chronic condition in which progression to AIDS is increasingly rare. Anthony Fauci, head of the United States National Institute of Allergy and Infectious Diseases, has written, "With collective and resolute action now and a steadfast commitment for years to come, an AIDS-free generation is indeed within reach." In the same paper, he noted that an estimated 700,000 lives were saved in 2010 alone by antiretroviral therapy. As another commentary in *The Lancet* noted, "Rather than dealing with acute and potentially life-threatening complications, clinicians are now confronted with managing a chronic disease that in the absence of a cure will persist for many decades.

There are six classes of drugs, which are usually used in combination, to treat HIV infection. Antiretroviral (ARV) drugs are broadly classified by the phase of the retrovirus life-cycle that the drug inhibits. Typical combinations include two nucleoside reverse-transcriptase inhibitors (NRTI) as a "backbone" along with one non-nucleoside reverse-transcriptase inhibitor (NNRTI), protease inhibitor (PI) or integrase inhibitors (also known as integrase nuclear strand transfer inhibitors or INSTIs) as a "base."

Entry inhibitors (or fusion inhibitors) interfere with binding, fusion and entry of HIV-1 to the host cell by blocking one of several targets. Maraviroc and enfuvirtide are the two currently available agents in this class. Maraviroc works by targeting CCR5, a co-receptor located on human helper T-cells. Caution should be used when administering this drug, however, due to a possible shift in tropism which allows HIV to target an alternative co-receptor such as CXCR4. In rare cases, individuals may have a mutation in the CCR5 delta gene which results in a nonfunctional CCR5 co-receptor and in turn, a means of resistance or slow progression of the disease. However, as mentioned previously, this can be overcome if an HIV variant that targets CXCR4 becomes dominant.

Nucleoside reverse-transcriptase inhibitors (NRTI) and nucleotide reverse-transcriptase inhibitors (NtRTI) are nucleoside and nucleotide analogues which inhibit reverse transcription. HIV is an RNA virus and hence unable to become integrated into the DNA in the nucleus of the human cell; it must be "reverse"

transcribed into DNA. Since the conversion of RNA to DNA is not done in the mammalian cell it is performed by a viral protein which makes it a selective target for inhibition. NRTIs are chain terminators such that once incorporated, work by preventing other nucleosides from also being incorporated into the DNA chain because of the absence of a 3' OH group. Both act as competitive substrate inhibitors. Examples of currently used NRTIs include zidovudine, abacavir, lamivudine, emtricitabine, and of NtRTIs tenofovir and adefovir.

The life cycle of HIV can be as short as about 1.5 days from viral entry into a cell, through replication, assembly, and release of additional viruses, to infection of other cells. HIV lacks proofreading enzymes to correct errors made when it converts its RNA into DNA via reverse transcription. Its short life-cycle and high error rate cause the virus to mutate very rapidly, resulting in a high genetic variability. Most of the mutations either are inferior to the parent virus (often lacking the ability to reproduce at all) or convey no advantage, but some of them have a natural selection superiority to their parent and can enable them to slip past defenses such as the human immune system and antiretroviral drugs. The more active copies of the virus, the greater the possibility that one resistant to antiretroviral drugs will be made.

Antiretroviral drug treatment guidelines have changed over time. Before 1987, no antiretroviral drugs were available and treatment consisted of treating complications from opportunistic infections and malignancies. After antiretroviral medications were introduced, most clinicians agreed that HIV positive patients with low CD4 counts should be treated, but no consensus formed as to whether to treat patients with high CD4 counts.

There is a consensus among experts that, once initiated, antiretroviral therapy should never be stopped. This is because the selection pressure of incomplete suppression of viral replication in the presence of drug therapy causes the more drug sensitive strains to be selectively inhibited. This allows the drug resistant strains to become dominant. This in turn makes it harder to treat the infected individual as well as anyone else they infect.