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HIV/AIDS eradication

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ABSTRACT

Antiretroviral therapy can inhibit HIV replication in patients and prevent progression to AIDS. However, it is not curative. Here we provide an overview of what antiretroviral drugs do and how the virus persists during therapy in rare reservoirs, such as latently infected CD4+ T cells. We also outline several innovative methods that are currently under development to eradicate HIV from infected individuals. These strategies include gene therapy approaches intended to create an HIV-resistant immune system, and activation/elimination approaches directed towards flushing out latent virus. This latter approach could involve the use of novel chemically synthesized analogs of natural activating agents.

Beginning with its first transmission into humans from chimpanzees approximately 100 years ago,[1] human immunodeficiency virus (HIV) has had a devastating effect throughout the world. At the end of 2011 an estimated 34 million people were living with HIV, and in that year approximately 1.7 million people died of acquired immunodeficiency syndrome (AIDS).[2] There is currently no vaccine to prevent HIV infection, and while efforts to develop such a prophylactic vaccine are beginning to show promise,[3] it is a complex challenge which is unlikely to be achieved in the near future. Significant advances for treating HIV have been made in the area of antiviral therapy. However, these treatments are expensive and can result in side-effects, adherence issues, and the development of drug-resistant virus. Most importantly, they are not curative, and must instead be taken for the remainder of the patient's life to effectively contain the virus and prevent progression to AIDS. Furthermore, access to such drugs is limited for individuals in many parts of the world.[2] Developing a cure for HIV to eliminate the virus from people who are already infected is therefore an important area of research. The purpose of this review is to describe what currently available HIV therapies do, outline our understanding of why they do not cure the infection, and discuss several novel approaches that are currently under development for eliminating HIV from infected individuals.

HIV infects and kills cells of the immune system, including CD4+ T cells and macrophages.[4] These cells are critical for mounting effective immune responses against invading pathogens. Over time, HIV replication causes depletion of these cells, leading to lower total CD4+ T cell numbers, damage to the architecture of lymph nodes and other lymphoid tissues, immune activation, and general dysregulation of immune function.[4] After an average infection time of around 10 years, the immune system is damaged to the point that the infected individual progresses to AIDS. At this stage the individual becomes highly susceptible to both common and unusual infections and cancers, which ultimately result in death.[4]

Since HIV replication is required for the development of disease, antiretroviral drugs have been developed to prevent this replication and stop progression to AIDS.[5] A diagram outlining the major steps in the HIV life cycle and the targets of clinically approved antiretroviral drugs is shown (Fig. 1). As a retrovirus, the genetic material in HIV virions (virus particles) is RNA, but the virus replicates through a DNA intermediate that is integrated into the DNA of the host cell. During infection, the virus first binds to the CD4 protein and a coreceptor protein at the cell surface. The most commonly utilized coreceptors are the chemokine receptors CCR5 and CXCR4, with CCR5 usage generally predominating in early infection, and often maintained throughout infection.[6] The viral and host cell membranes then fuse, and the virion-borne reverse transcriptase enzyme catalyzes conversion of the viral RNA into DNA. This DNA is transported into the nucleus as part of a pre-integration complex. The viral integrase enzyme then mediates the integration process, whereby the viral DNA is inserted into the host

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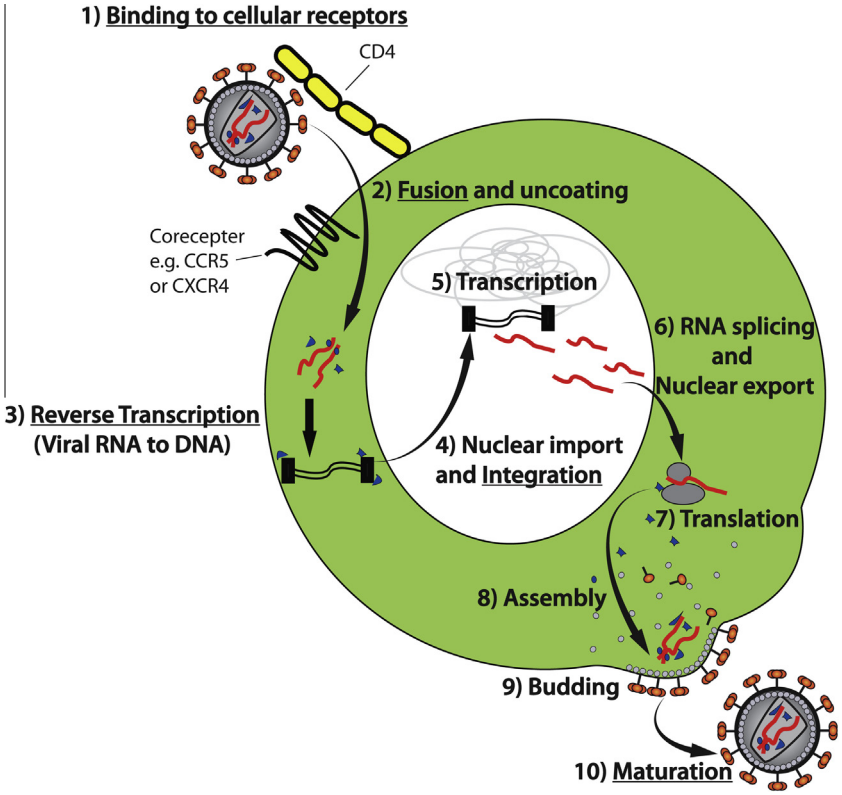

Figure 1. Essential steps in the HIV life cycle and targets of currently available antiretroviral drugs. (1) HIV virus particles (virions) bind to CD4 and a coreceptor (generally CCR5 or CXCR4) on target cells. (2) The viral envelope proteins mediate fusion of the viral and host cell membranes, allowing the viral RNA to be released into the host cell cytoplasm. (3) The viral RNA is reverse transcribed into double stranded DNA by the HIV reverse transcriptase enzyme. (4) Double stranded viral DNA is translocated into the nucleus and the HIV integrase enzyme catalyzes integration of this DNA into the host cell's chromosomes. At this point the HIV genome is referred to as 'proviral DNA' or an 'integrated provirus'. (5) Transcription of the HIV genome is mediated by host cell polymerases. (6) and (7) HIV RNA is exported to the cytoplasm for translation or incorporation into new virions. For expression of some proteins, the RNA is spliced prior to nuclear export. (8) and (9) New virions assemble and bud from the plasma membrane. (10) As virions bud, the viral protease enzyme cleaves HIV polyproteins into individual subunits, producing infectious, mature virions. Underscored steps represent those that are targeted by clinically-approved antiretroviral drugs.

cell's chromosomes. At this point the resultant proviral DNA is permanently integrated and will be maintained for the lifespan of the host cell. HIV RNA is then transcribed from the integrated provirus, and is either translated into proteins (following RNA splicing for certain viral proteins), or directly incorporated into new virions. The virions assemble and bud from the plasma membrane. Finally, the viral protease enzyme cleaves polyproteins within the virion to produce mature infectious virus particles that are ready to infect a new cell.

Over 20 antiretroviral drugs have been approved for use in HIV infected patients.[5] These drugs variously inhibit virus entry (fusion/entry inhibitors), reverse transcription (reverse transcriptase inhibitors), integration (integrase inhibitors), or maturation (protease inhibitors) (Fig. 1). Modern antiretroviral therapy regimes typically consist of specific combinations of three antiretroviral drugs termed combination antiretroviral therapy (cART) or highly active antiretroviral therapy (HAART). The rationale behind using multiple drugs with non-overlapping resistance profiles is to increase the suppression of virus replication achieved by the therapy while also reducing the likelihood of the virus becoming resistant to the drugs. Importantly, these antiretroviral drugs only inhibit virus replication. Therefore they can stop the virus from spreading to new cells but have no direct effect on an integrated HIV provirus.

Untreated HIV infection is generally characterized by a continuous battle between the virus and the host immune response, with billions of new virions and infected cells produced and cleared every day (Fig. 2).[7] The fact that the adaptive immune response maintains much of its function for years during this onslaught is a testament to its strength and regenerative capacity. Treatment with HAART eliminates the vast majority of (or potentially all) HIV replication, and plasma viral loads often fall to levels that are undetectable with standard clinical assays (such assay limits are typically 50 copies of virion RNA/ml of plasma).[4] However, certain reservoirs of replication-competent virus persist during therapy. Therefore if HAART is stopped then virus can emerge from these reservoirs and rapidly spread,[8] causing renewed progression towards AIDS. The resultant rebound in plasma viral loads typically occurs within several weeks of stopping therapy, indicating that virus is being released from reservoirs with regularity.[9]

The best understood reservoir of HIV during HAART consists of latently-infected CD4+ T cells. These cells are resting (primarily central and transitional memory) CD4+ T cells that harbor an integrated HIV provirus and express little or no viral RNA and no viral proteins, but can be induced to produce infectious virus if the cell becomes activated.[10–13] In this non-expressing state the latent provirus cannot be recognized by the immune system, and consequently the infected cell is not eliminated by immune effector mechanisms. Latently-infected CD4+ T cells are relatively rare in HAART-treated patients, with approximately 1 latently-infected cell per million total resting CD4+ T cells, translating into about one million latently-infected cells per patient.[14] These memory CD4+ T cells are a key component of immunological memory responses, and it is believed that they can survive for decades even while harboring latent HIV proviruses. The stability of this reser-