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CURRENT TRENDS IN ANTIRETROVIRAL THERAPY FOR HIV INFECTION AND AIDS

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HIV-1 Infects CD4+ T-lymphocytes and macrophages. Studies of viral kinetics indicate a very high replication rate, with a viral life-cycle of about 1.6 days. It has been estimated that 99% of the HIV RNA in plasma (viral load) is produced by cells that were infected within the previous 48-72 hours, and that up to one billion ($1x\ 10^9$) CD4+ T-cells are produced per day in response to the infection. High- level **viremia** occurs shortly after primary infection and eventually a "set point" is established for the level of HIV RNA in plasma, reflecting the balance between HIV-1 replication and the antiviral cellular immune response. With time, however, there is a progressive decline in **CD4+ T-cells** and the patient suffers **from acquired immune deficiency** and is at risk of developing opportunistic infections and AIDS-associated neoplasias.

Antiretroviral drugs, whether nucleoside reverse transcriptase inhibitor (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (Pls), all target critical steps in the viral replication cycle, in order to suppress viral replication. This lowers the **"viral load"** (or vital burden) and allows for at least partial immune reconstitution over time.

The experiencie of over a decade of clinical trials in HIV-infected patients indicates: 1) Monotherapy with any retroviral drug is only transiently effective in suppressing HIV-1 replication due to the emergence of resistant viral strains. 2) **Combination therapy** using at least 2 NRTIs (i.e. zidovudine and lamivudine) plus protease inhibitor (i.a. indinavir) is clearly superior to the monotherapy with a protease inhibitor or combination therapy with 2 NRTIs. Some regimens combining 2 NRTIs with one NNRTIs (i.a. efavirenz) also appear effective. A variety of **"salvage regimens"** are under study to treat patients failing the current 3-drug combination regimens, including regimens combining 2 Pls. Hydroxyurea (used in the treatment of some hematologic malignancies and sickle-cell disease) is now also under study in patients with HIV infection, since it can potentiate the action of the NRTI didanosine and may also impact latent viral reservoirs in lymphoid tissue.

Effective combinations of antiretroviral drugs that can suppress viral replication and drive the plasma HIV RNA levels below the limits of detection with current methodology, are referred to as **"highly active antiretroviral therapy"** or "**HAART**". A critical issue for the long term management of HIV- infected patients is the "durability" of the response (months or years). Response to therapy can be assessed by parameters such as weight gain and feeling of well being while on HAART, but primarily through the use of **"surrogate markers"** of disease activity such as the CD4+ T-cell count and the plasma HIV RNA levels. For example, patients with less than 200 CD4+ cells per mm^3 are at risk of suffering opportunist infections like *Pneumocystis carinii* pneumonia or cerebral toxoplasmosis. Effective treatment with HAART is usually associated with a rise in the CD4+ T-cell count, although complete restoration of cellular immunity has not been demonstrated. Effective treatment with HAART should also lead to plasma viral load of less than 200 copies of HIV RNA per ml. The likelihood of long-term suppression of viral replication is enhanced if HAART leads to a plasma viral load of less than 50 copies of HIV RBNA per ml. Clinical endpoints of disease progression include the occurrence of opportunistic infections, weight loss (the "wasting syndrome")AIDS- associated malignancies (CNS lymphomas, Kaposi's sarcoma) and HIV- related neuropathy and encephalopathy ("AIDS dementia"), ultimately resulting in death.

The use of antiretroviral drugs is often limited by side-effects and **toxicities** like anemia, neutropenia (zidovudine, stavudine, other NRTIs), peripheral neuropathy (didanosine, stavudine, zalcitabine) pancreatitis (didanosine), Fanconi's Syndrome (adefovir), allergic reactions (nevirapine, delavirdine, efavirenz), nephroli-thiasis (indinavir), glucose intolerance and lipodystrophy (all the protease inhibitors), such that treatment may be interrupted or permanently discontinued due to these toxicities.

Patients **adherence** to the prescribed therapeutic regimen is essential in order to maintain adequate **"drug exposure"**(an effective area-under-the plasma concentration-time curve or AUC) and suppression of viral replication. It is now recognized that **"therapeutic failure"** is not always the result of emerging viral resistant strains, but may be due to inadequate drug dosing and lack of adherence to therapy.

Treatment with effective drug combinations is also influenced by **drug interactions** (mostly related to CYP3A4, the main isozyme involved in the metabolism of the protease inhibitors). For example, the use of rifampin in a patient with HIV and tuberculosis (frequent opportunistic infection in patients with AIDS) may lead to reduced plasma levels of the protease inhibitor and loss of viral suppression, due to the enzyme-inducing action of rifampin in the liver. On the other hand, combining the protease inhibitor ritonavir (an inhibitor of CYO3A4) with another protease inhibitor like saquinavir, may lead to greatly increased levels of the latter.

New classes of drugs are under development, notably pentafuside (T20) and T-1249, both of which are **viral fusion inhibitors** blocking the interaction of the HIV envelope gp41 with the target cell membrane. Finally several clinical trials have shown the value of combining HAART with Interleukin-2 (IL-2) to stimulate a rise in CD4+ T-lymphocytes, thus enhancing the probability of **immune reconstitution.**