

# [Anti-retroviral treatment of hiv aids](https://assignbuster.com/anti-retroviral-treatment-of-hivaids/)

The causative agent for Acquired immunodeficiency syndrome AIDS is the Human Immunodeficiency virus HIV. These are diploid and enveloped, single-stranded, positive-sense RNA viruses, which have the ability to integrate viral genome that persists within the host-cell DNA through viral intermediate copy DNA (cDNA)[1].

They are retroviruses with 2 structurally related forms HIV-1 and HIV-2.

The diploid positive single-strandedRNAcodes for the ninegenesenclosed by a conicalcapsid. The nine genes are used to code for the proteins and enzymes used for replication. The three main genes are the gag, the pol, and env. It is known that the gag gene is responsible for coding the core proteins in the viral particle whilst the pol gene encodes the enzymes protease, reverse transcriptase, and integrase. The env gene holds the codes with which the HIV structural glycoproteins are manufactured. The rest of the genes—rev, nef, vif, vpu, vpr, and tat—are important for viral replication and mostly responsible for HIV’s penetrance and infectivity rate[1].

The difference between HIV 1 and 2 is the absence of vpu in HIV 2

The three major enzymes produced by the virus are important for functioning at different times during the replicative cycle. Therefore theses enzymes are the target of pharmacologic blockade as antiviral therapy. The RNA-dependent DNA-polymerase (with its RNase H function) acts mostly in the initial phases of viral replication to form a double-stranded DNA or copy DNA of the virus RNA. The integrase then act within the cell nucleus to integrate the viral cDNA into the host chromosomal DNA.

The Protease enzyme functions by processing the Gag and Gag-Pol polyproteins during maturation of the viral particle either at the cell surface or at the budding viron[1].

Despite considerable progress in research into the virology of HIV as elucidated above, some of the specific details of the pathologic process that leads to AIDS have not been fully understood especially the reactive immune response of the human host, which is the driving force for the quest to a much better understanding of the AIDS.

What is noted is that there is a noticeable decline in the CD4 + helper T cells, which results in the reversal of the CD4/CD8 T-cell ratio which affects adversely the regulation and production of B-cell antibody. This result in a reduction of both cellular and humoral immune responses to certain antigens and inadequate response of the host to opportunistic infections and otherwise normally harmless commensal organisms. However, the defect overwhelmingly affects cellular immunity more, the infections tend to be mycobacterial, fungal, or viral [2].

Despite the above understanding and targeted blockade of the understood processes of viral replication, there has not been adequate control of viral load commensurate with intervention. Direct blood injection and inoculation and genital/anal exposure are the main portal of entry for HIV infection, the GI tract which is laden with a vast amount of lymphoid tissue, has been noted to be an ideal site for HIV replication. It is now believed that most of the initial processes of HIV infection are derived [3].

Therefore, Gut Associated Lymphoid Tissue or GALT, is an important site of early viral concentration and replication leading to a significant pro-viral reservoir. It is strongly believed that this reservoir is mostly responsible for the difficulty in efforts to reduce the levels of HIV provirus through sustained treatment with antiretroviral drugs[4]

The GALT is compartmentalized, and this provides an additional feature of HIV replication and reservoir even among different segments of the gastrointestinal tract. Measurements of CD4 + T cells in GALT has shown lower effect of antiretroviral therapy than that noted in corresponding peripheral blood [4].

One hypothesis explaining the above discrepancy is that there is continous viral replication in the gut lymphoid tissue, and the ensuing trigger of an immune response involved, may actually adversely affect efficient CD4 + T-cell replenishment [5].

Right from the onset, after HIV was identified in 1985, Cooper and colleagues described the clinical features of acute HIV infection . A virus-like illness by recently infected individual can present within 1 to 3 weeks. Symptoms consist of headache, sore throat, muscle aches, retro orbital pain, with low-grade or high-grade fever, and swollen lymph nodes, and most times a non pruritic macular erythematous rash involving the trunk and, later, the extremities [6].

In some cases, oral candidiasis and ulcerations in the esophagus or anal canal occur, and central nervous system disorders can be seen (e. g., encephalitis.

Children will most often with the common bacterial infections of childhood like pneumonia, otitis media and sinusitis. These can be more severe and occur more frequently than similar infections in immunologically competent children.

In children infected by mothers through pregnancy (vertical transmission) with HIV become symptomatic from the neonatal period up to age 8 years and that 57% of this group have associated disease within the first year [7].

A panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children in 2010 made recommendations for diagnosis of HIV in infants as follows [8]:

* Due to the fact that maternal HIV antibody persists up to 18 months, infants younger than 18 months require direct virologic assays that detect HIV to make a diagnosis of HIV infection
* The recommended virologic assays include the HIV bDNA Polymerase Chain Reaction and HIV RNA assays
* Additional testing is recommended in infants with exposure to HIV in the perinatal period, at 14 days, at 1 month, and at 4 months.
* After age 18 months, regular HIV antibody assays can be used for diagnosis

Continous monitoring of the CD4 + levels or percentages in patients newly diagnosed with HIV.

The 2010 Panel recommends that in children younger than 5 years, using CD4 percentages every 3- to 4-months to monitor patients’ immune status and disease progression due to the fact that absolute CD4 counts tends to vary with age [8].

CBC count with differential and a urinalysis is done every 1-3 months in infants

If the mother is HIV positive, the recommendation is to use appropriate serologic screening tests to check for hepatitis C, hepatitis B, toxoplasmosis, and syphilis.

Features of HIV that affect the anti-retroviral treatment modalities[8];

* Integrated virus can be latent and can remain unaffected by the immune response
* Virus can spread by cell-to-cell transfer
* Infected cells are a major source of HIV transmission and pathogenesis
* Infected T cells, B cells, and macrophages can be circulating reservoirs for HIV; tissue macrophages and GALT cells can be resident reservoirs that persistently release virus
* Virus can infect brain cells (astrocytes and oligodendrocytes); therapy must pass the blood-brain barrier
* Virus can escape neutralizing antibodies; in some cases, virus infection is sensitive to enhancement by antibodies
* Antigenic variations occur widely among HIV-1 and HIV-2 strains
* Sequence mutations can occur early in the regions coding for the HIV envelope and regulatory genes
* Opportunistic infections, such as candidiasis, herpes and varicella-zoster virus infection, should elicit high index of suspicion, and appropriate prophylactic treatment strategies deviced.

Anti Retroviral Therapeutic agents or ARTs has been and remains the most important aspect of human immunodeficiency virus (HIV) treatment.

In 1987 the first drug, the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (AZT), was approved for use in patients infected with HIV. Seven other drugs in this class followed and other classes were introduced.

There are six broad groups of ARTs [9].

* Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)
* Protease inhibitors (PIs)
* Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
* Fusion inhibitors
* CCR5 co-receptor antagonists (entry inhibitors)
* HIV integrase strand transfer inhibitors

The current general recommendation for an initial ART regimen includes two NRTIs and a third drug from a different class [8. 9].

For of infected infants, children, and adolescents, combination ART (cARTs) with at least 3 drugs from at least 2 classes of drugs is recommended for initial treatment because it provides the best opportunity to inhibit viral transcription, yet preserve immune function by delay in disease progression.

NRTIs stop HIV replication by terminating the transcription of viral RNA to DNA via a viral encoded protein reverse transcriptase

RTIs (NRTIs & NNRTIs) also inhibit human DNA polymerase including mitochondrial DNA (mtDNA) which results in depletion of mtDNA and drug-related toxicities. These toxicities can be life-changing and include diabetes mellitus, peripheral neuropathy, lipodystrophy, pancreatitis, myopathies, renal tubular acidosis, and steatohepatitis, [8, 9].

Protease Inhibitors block the formation of the core structural proteins of the virus in the late stages of viral replication.

Children with HIV Early Antiretroviral Therapy trial or CHEAT trial, showed that early intervention and treatment with ART led to a 75% reduction in HIV progression and moreso a 76% reduction in infant mortality [10].

* It is recommended that treatment be initiated in children aged 12 months or older who have mild symptoms or asymptomatic or and have a CD4 of 25% or more.
* Also children who are 1-4 years of age with more than 350 cells/μL
* And in children aged 5 years or older who have plasma HIV RNA of 100, 000 copies/mL or more.

The biggest challenge in the management of children with HIV infection is the compliance to the regimen. Hence some regimen and/or dosing frequency may clearly constitute a burden for younger children..

So studies looking into the use of a simple once daily cART regimen may therefore be a powerful solution to optimize treatment adherence and the patient’s quality of life [11].

The only preferred regimens for children younger than 3 years are co formulated lopinavir/ritonavir-based therapy and nevirapine-based therapy

Another viable solution to the issue of compliance is a fast and efficient reduction of the viral load using medications known as highly active ART (HAART) which will significantly slow viral replication and prevent resistant mutations from developing [8].