# CURRENT CONCEPTS IN THE DRUG TREATMENT OF HIV/AIDS.

**Essien E.M.**

*Professor E.M. Essien, MD, FMC Path, FRC Path, FAS, FTWAS, is of the Department of Haematology & Immunology University of Port Harcourt, Nigeria.*

**Introduction**

Since the first reports were made in 1981 of AIDS among some American young male professionals who were all homosexuals, the infection has become a pandemic and now appears to affect poor countries most seriously. Shortly afterwards, its causative agent, the human Immunodeficiency virus (HIV) a retrovirus, was discovered and its essential biology including molecular biology, epidemiology, pathogenesis and diagnostic elements and technology were described and developed. Although these fascinating developments have taken place in such a very short time interval and we therefore have considerable knowledge about the characteristics of the epidemic and its trend compared with past epidemics (Cartwright & Biddis 1972), we have however, not made as much progress with treatment of Aids in its many manifestations as we ought to have done. The reason for this difficulty is the puzzling rapidly mutation capability of the retrovirus, an organism that previously and in its natural habitat, was a very stable organism and whose close relations retain that stable characteristic. One result of the above feature of the organism is that we neither have an effective preventive vaccine despite claims to the contrary, therapeutic vaccines nor drugs that are effective, affordable to all AIDS patients everywhere, and are not so toxic (Cohen 1999, World Federation of haemophilia (WFH), 1998). Several candidate vaccines, 27 to date (NIAID 2000) and drugs have, despite the above comments, been tested and tried and are being extensively used.

**Available Drugs and Therapeutic Regimes**

These drugs are based on the known biology of the retrovirus but none of them can completely eliminate the virus from host tissues. However, combinations of agents from the different categories of drugs (see below) have been shown to decrease viral replication, improve immunological status and delay super infection with other organisms, including opportunistic infective organisms. As a result of all the above, the patient survive longer (Carpenter et al 1997; World Federation of Haemophilia (WFH 1998). The different categories into which commonly used anti-retroviral drugs are classified are (a) Nucleoside Reverse Transcriptase inhibitors such as Zidovudine (AZT), Didanosine or Stavudine. A sub-group of drugs in this category comprises those agents that can inhibit viral replication but are non-nucleoside reverse transcriptase inhibitors. They act synergistically with Zidovudine. Examples in this sub-group are Nevirapine and Delavirdine. The other large category of anti-retroviral drugs are the Protease inhibitors such as Saquinavir (Invirase). Indinavir (Crixivan) etc. The Protease inhibitors prevent cleavage of protein precursors, a step in HIV protein synthesis that is essential for its maturation and subsequent infection of new cells and viral replication within such cells. This list of drugs is summarised in table 1. A new group of drugs based on their ability to inhibit HIV attachment to target cells in vivo is almost in the market. It is certain that newer drugs will still be developed.

**Drug Resistance:**

As has been the experience with antibiotics and some anti-tumour drugs, strains of HIV-1 (this has been most studied), which have developed resistance to both categories of drugs, have been described. One way of slowing down this trend is to use drug combinations such as for instance, Zidovudine (a nucleoside reverse transcriptase) with Saquinavir (a protease inhibitor). This particular drug combination has the advantage in that it is effective against HIV-1 strains that were already resistant to Zidovudine. Great care is required in selecting what drug combinations that should be used because of (a) overlapping toxicity (b) rapid onset of resistance with some drugs and (c) high costs (see below).

**Drug toxicity:**

This is common with all retroviral drugs and have, in addition to cost considerations, severely limited the use of these agents (see table 2). For instance anaemia, Neutropenia, nausea, vomiting, headache, fatigue, confusion, malaise, myopathy and hepatitis are known toxic effects of Zidovudine. Lactic acidosis is a rare but commonly fatal toxic effect of this drug. However, its use in pregnant women after the first trimester to prevent or reduce mother-to-child transmission of HIV, has not resulted in foetal malformation (Newell et al 1997). In this respect, it needs to be emphasised that any assessment, data collection or system evaluation involving pregnant Nigeria women that ignores this critical information is not justified.

**Drug treatment of HIV infection in pregnant women.**

A major consideration in this respect is to reduce mother-to-child transmission. This should be undertaken after the first trimester. One regime recommends Retrovir to be given at 300mg bd from the 30th week of gestation till delivery, to be continued at 300mg/d for 6/52 afterwards. Another regime suggested is 200mg tid from week 14-34 of gestation; it is suggested that with this procedure, HIV-1 transmission rate has been reduced from 20% to 8% (Connor et al 1994). Still others prefer a combination therapy such as that with Zidovudine + Lamivudine.

**Drug Combinations**

It is now common practice to use drug combinations such as nucleoside reverse transcriptase inhibitors, a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor or other combinations. This strategy reduces the risk of onset of drug resistance, enhances efficacy in reduction of viral load and reduces both the incidence and severity of toxic effects. The rationale in the latter situation is that reduced dosages can be introduced. However, combination of AZT and Stavudine, both

in the same category, is not recommended but a replacement of one by the other has been used.

**Nutritional Supplements**

This is a very important component of good management of HIV infection. For instance, some alternative HIV treatment strategies such as that of Lyn Francis in Zimbabwe, strongly promote good nutrition and claim improvement in clinical status and survival. This makes good sense in a clinical situation of associated very severe weight loss that is partly due to marked gastro-intestinal disturbances.

**Duration of treatment, Cost implications and other issues**

The above indicate good progress that have been achieved in our understanding of the biology of HIV, the pathogenesis of its different disease manifestations, and progress in its treatment. It has been estimated that the HIV drug will costs N30,000 - N70,000 monthly to treat each patient effectively (Mohammed, 1. Personal communication). Based on studies of decay characteristics of HIV load in blood plasma and other tissues such as lymphnodes, it will required 2.3 - 3.1 years of effective combination therapy to approximately "eliminate" HIV-1 from the body (Perelson et al 1997). Some workers recommend treatment for life, this means costs which only very few patients can bear; even at treatment for 2-3 years.

There is in addition to the above, the very basic question of why the average African appears to be so easily susceptible to HIV infection. It is obvious that it cannot be only the sex story. This and other questions demand our serious research attention, and activity that has been seriously lacking since the beginning of the epidemic in Nigeria about 1985-6.

**Other treatment Components:**

Other aspect of HIV patients management include vigorous treatment of opportunistic and other infections which are usually very common in the infection. The management of haematological, neuro-psychiatric and other complications should be equally vigorously pursued as should involvement of the community including patient re-integration into the community.

**Summary**

This short paper focuses on, and summarizes drug treatment of HIV/AIDS specifically. Brief references are made to the other management aspects of the problem such as vigorous treatment of opportunistic infections and haematological and neuro-psychiatric complications. Attention is drawn to the need for re-integration of the patient into their respective communities. Finally, the need for us to conduct serious research into all aspects of the pandemic as it affects us, is emphasised.

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**Table 1**

** Some available drugs commonly used in HIV infection

| Category | Agents | Dosage |
|---|---|---|
| Nucleoside Reverse Transcriptase inhibitors | Zidovudine (AZT) | 200mg tid oral |
| | Stavudine (d4T) | 40mg bd oral |
| | Didanosine (ddI) | 200mg bd oral |
| | Lamivudine (3TC) | 150mg bd oral |
| | Zalcitabine (ddc) | 0.75mg tid oral |
| | Zidovudine +](Combivir) Lamivudine ] | 1 tab bd oral |
| Non-nucleoside reverse transcriptase inhibitors | Nevirapine (Viramine) | 200mg bd oral |
| | Delavirdine (Rescriptor) | 400mg bd oral |
| Protease inhibitors | Saquinavr (Invirase) | 600mg tid oral |
| | (Fortovase) | 200mg tid oral |
| | Indinavir (crixivan) | 800mg 8hry oral |
| | Ritonavir (Norvir) | 600mg tid oral |
| | Nelfinavir (Viracept) | 750mg tid oral |

NB: There are several critical limitation to the use of the drugs. For example, patients with <60kg body weight should take Stavudine 30mg bd. Similarly with Nevirapine, the starting dose should be 200mg/d x 2/52 to reduce the risk of developing skin rash.

It is now common practice to use the drug in combination in order to reduce onset of drug resistance and with lowered dosage to reduce toxicity.

**Source: The Medical Letter of Drugs & Therapeutics Dec. 1997. See updates for additional and new information.

**Table 2:**

**Summary of toxic effects of some drugs used in the treatment of HIV**

| Drug | Toxic Effect |
|---|---|
| Satvudine | Peripheral Sensory neuropathy |
| | Increased Serum aminostransferase |
| | Pancreatitis (rare) |

| | |
|---|---|
| Didanosine | Peripheral neuropathy (dose-related)<br>Gastro-intestinal disturbance<br>Pancreatitis<br>Lactic acidosis (often severe)<br>Retinal depigmantation |
| Lamivudine | Uncommon.<br>Neuropathy may occur |
| Zalcitabine | Peripheral neuropathy (dose related) especially in Diabetics.<br>Fever<br>Skin Rash<br>Stomatitis<br>Pancreatitis<br>Oesophagitis |
| Nevirapine | Skin Rash, Can → Stevens Johnson Syndrome<br>Fever<br>Nausea<br>Headache |
| Delavirdine | Skin rash ++ Disappears on discontinuation. Can be restarted |
| Saquinar | Diarrhoea<br>Nausea<br>Abdominal pains<br>Serum aminotransferase |
| Indinavir | Heamolytic anaemia<br>Hepatitis<br>Crystalluria with dysuria<br>Back & flank pain but no frank nephrolithiasis. |
| Ritonavir | Nausea and Vomiting, diarrhoea<br>Circumoral & Peripheral paraesthesia<br>Renal failure<br>Aesthenia<br>Hypertriglyceridemia, hypercholesterolaenia |
| Nelfinavir | Diarrhoea |