Open Access Journal

International Journal of Medical Research and Pharmaceutical Sciences

February 2015, Volume 2(Issue 2) ISSN: 2394-9414

EVALUATION OF THE THERAPEUTIC EFFICACY OF ANTIRETROVIRAL DRUGS USED IN THE CLINICAL MANAGEMENT OF HIV/AIDS INFECTION

Anochie, P.I[*1], Onyeneke, E.C[2], Onyeozirila A.C[3], Asowata E[4], Okoihue A4, Ogu A.C5 and Afocha E[*1]

[*1]TB/HIV/AIDS Research group, Nigerian Institute of Medical Research, Yaba, Lagos.
[2]St. Joseph's Hospital, Enyiogugu, Aboh Mbaise LGA, Owerri, Imo state Nigeria.
[3]Department of Medicine, Madonna University, Elele, Rivers state Nigeria,
[4]University of Lagos College of Medicine, University of Lagos Nigeria.
[5]Department of Medicine, University of Sheffield, Sheffield, UK.
[*1]ip.anochie@nimir.gov.ng

Keywords:
Evaluation, Therapeutic, Efficacy, Antiretroviral, Drugs, Management, HIV/AIDS, Infection

Abstract

The protease inhibitors are potent antiretroviral drugs because the protease activity is absolutely essential for production of infectious viruses. The newest class of drugs is the fusion inhibitors that blocks virus entry into cells. Persistent virus production is facilitated further by sub-inhibitory drug levels in infected cells or by host immune failure. Therefore, Pre-existing or newly produced drug resistant mutants can emerge that have a selective advantage under drug pressure. These escape mutants become dominant in the virus population and lead to viral rebound and therapy failure. This review provides knowledge for improvement of antiretroviral drug administration programmes.

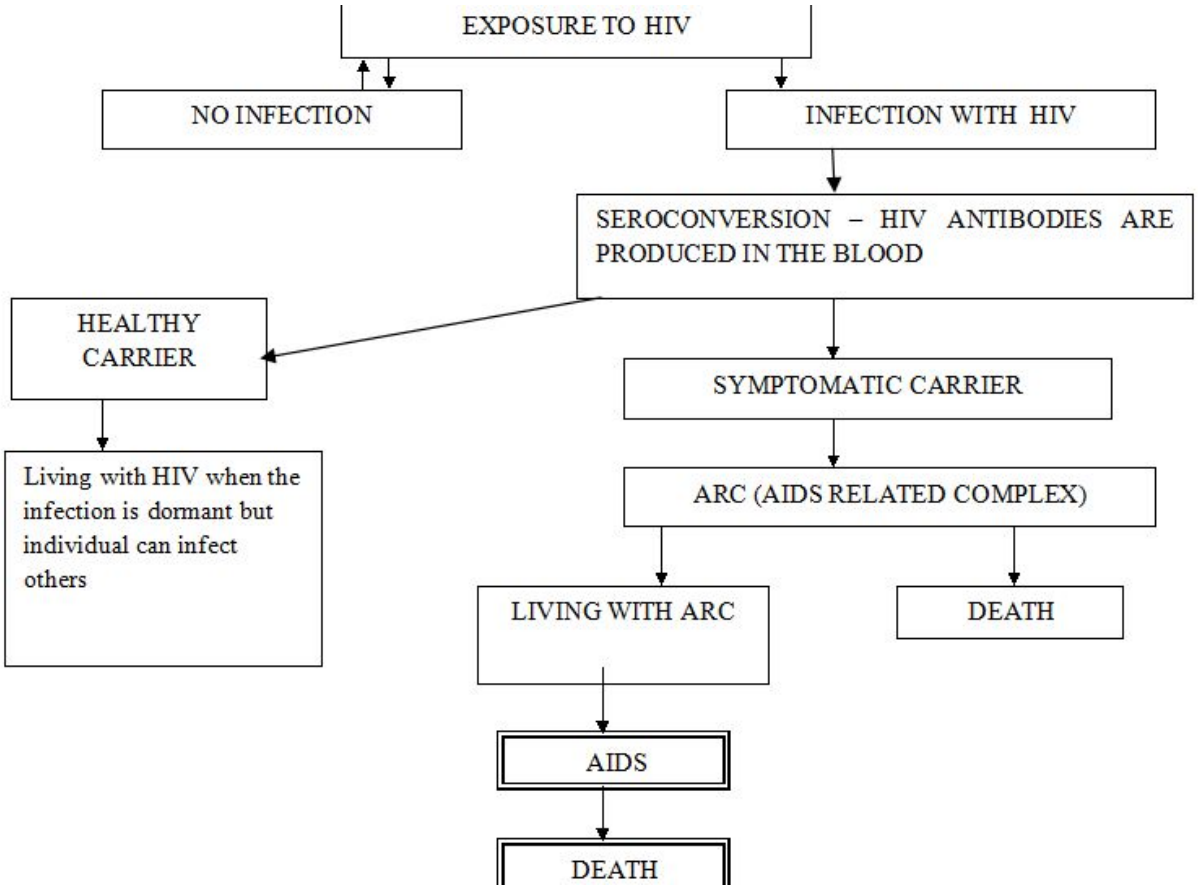
INTRODUCTION

Human immunodeficiency Virus (HIV) is a member of the genus Lentivirus, part of the family of Retroviridae (International Committee on Taxonomy of Viruses, 2006). Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry of the target cell, the viral RNA genome is converted to double-stranded DNA by a virally encoded reverse transcriptase that is present in the virus particle.

The viral DNA is then integrated into the cellular DNA by a virally encoded integrase, along with host cellular co-factors (Smith *et al*, 2006), so that the genome can be transcribed.

Once the virus has infected the cell, two pathways are possible: either the virus becomes latent and the infected cell continues to function, or the virus becomes active and replicates and a large number of virus particles are liberated that can then infect other cells. A schematic diagram of progression of HIV infection and its possible outcomes is illustrated in the figure below.

Fig 1: Possible outcomes of HIV infection



HIV is the etiological agent of AIDS. The illness was first described in 1981 and HIV-1 was isolated by the end of 1983 (Jawetz, 2007). If left untreated, vast majority of HIV infected individuals develop fatal opportunistic infections as a result of HIV in the immune system (Ademola, 2004)

Antiretroviral drugs are drugs used to suppress the HIV replication and boost the immune system. The drugs bring down the viral load to undetectable value of <50 copies/ml (Montessori *et al*, 2004). The classes of drugs include both nucleoside and non-nucleoside inhibitors of the viral enzymes-reverse transcriptase and inhibitors of the viral protease enzymes (Ademola, 2004). The protease inhibitors are potent antiviral drugs because the protease activity is absolutely essential for the production of infectious viruses. The newest class of drugs is the fusion inhibitors that blocks virus entry into cells. Therapy with combination of antiretroviral drugs referred to as highly active antiretroviral therapy (HAART) became available in 1996. It often times suppress viral replication to below limits of detection (<50 copies/ml), decrease viral loads in lymphoid tissue, allow the recovery of immune response to opportunistic pathogens and prolong patient survival. However, HAART has failed to cure HIV-AIDS infection. The virus persists in reservoirs of long-lived and latently infected cells. When HAART is discontinued or there is treatment failure, virus production rebounds. Whereas monotherapy usually result in the rapid emergence of drug-resistant mutants of HIV, combination therapy, which targets multiple steps in virus replication usually, delays selection of HIV drug resistant mutants, however mutants are also developed. Results with combination therapy have been successful and turned HIV infection into a chronic, treatable disease. Prolonged suppression of viral replication can be achieved along with restoration of immune function (DHHS, 2004). Current drug regimens are

often complicated and expensive; cannot be tolerated by all patients because of its side effect and lead to a number of treatment failure. The first once daily pill that combines three therapy was approved in the United States in 2006. Zidovudine (AZT) can significantly reduce the transmission of HIV from mothers to infants. A regimen of AZT therapy of mother during pregnancy and during birth process and of the infant after birth reduced the prenatal transmission by 65-75%. The majority of infected persons worldwide do not have access to any HIV drug (WHO, 2003).

This review evaluates the therapeutic efficacy of antiretroviral drugs which will provide knowledge for healthcare providers for the significant improvement and enhancement of the quality of antiretroviral drug administration programmes on HIV/AIDS patients.

ANTIRETROVIRAL DRUGS USED IN HIV/AIDS

Clinical Management

Drug treatment for HIV offer many people the chance to control the virus and stay healthy for much longer. It controls the virus by stopping it from replicating inside the body. Generally, the virus gets into the body cell and starts to make copies of itself, which then spread out of that cell and into another. The drugs interfere with the chemicals that the viruses uses to make these copies, for example, the fusion inhibitors stops the HIV binding onto a new cell so it can no longer enter.

The treatment does not work equally as well for every one. They can have side effects and some people develop what is called drug resistance. Drug treatment for HIV is known as combined antiretroviral therapy (CAR) or sometimes, highly active antiretroviral therapy (HAART) (Dybul *et al* (2002).

The different drugs from at least 2 different groups are taken together, 2-4 times a day. One of the drug classes used in HAART is the nucleoside reverse transcriptase inhibitors (NRTIs), which commonly form the "backbone" of the antiretroviral cocktail. This class includes Zidovudine (AZT), Lamivudine, Didanosine (ddl), Stavudine (d4T), Abacavir (ABC) and the newly released nucleotide analogue tenofovir. Two NRTIs are often combined with one medication from the other classes, the non nucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs) and fusion inhibitors. The NNRTI class comprises nevirapine (NVP), delavirdine (DLV) and efavirenz (EFV). The protease inhibitors (PIs) (DHHS, 2004) and the NNRTI class comprises some tablets that now contain 2-3 different drugs. The advantages of these drug combination is that people do not need to take as many tablets each day.

TYPES OF ANTIRETROVIRAL DRUGS USED IN HIV/AIDS CLINICAL MANAGEMENT

The types of antiretroviral drugs includes the nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitor (PIs), Fusion inhibitors, Integrase inhibitors, Entry inhibitors and Maturation inhibitors.

NUCLEOSIDE REVERSE TRAMSCRIPTASE INHIBITORS (NRTIs).

These are nucleoside analogues that intracellularly prevents DNA elongation and viral replication. These drugs are triphosphorylated to become nucleotides and are then incorporated into the viral DNA chain by the viral reverse transcription (RT) enzyme. The RT catalyzes the incorporation of deoxynucleoside triphosphate (dNTPs), forming a negative –sense DNA strand, by using positive sense RNA as a template. The RT RNase activity catalyzes the degradation of the positive sense RNA from the negative sense DNA. This enzyme's DNA polymerase activity generates a second positive –sense DNA strand to form double-stranded proviral DNA(Shalom *et al*.,2003). Nucleoside reverse transcriptase inhibitors structurally resembles endogenous dNTPs, inhibiting the formation of viral DNA through two mechanisms. First,they competitively inhibit dNTPs for the RT enzyme. Second, once incorporated into the HIV DNA strand, their modified 3^1 hydroxyl group causes chain termination of DNA synthesis. Nucleoside reverse transcriptase inhibitors includes; Zidovudin (AZT), Lamuvidine (3TC), Didanosine (ddl), Stavudine(d4T) ,Abacavir (ABC).

NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

These are non nucleoside-analogue RTIs (NNRTIs) that distort the binding potential of the reverse transcriptase enzymes. Non-nucleoside RT inhibitors (NNRTIS) directly bind to the RT molecule. The NNRTIs are a structurally diverse group of compounds, with an aromatic structure, that bind to a hydrophobic pocket near the polymerase site of HIV RT. This group of dugs include: Nevirapine (NVP), Efavirenz (EFV), and Delavirdine (DLV),

PROTEASE INHIBITOR (PIs): This drug targets viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent protein for final assembly of new virus (Martin, 1991). Protease are responsible for post translational processing and cleavage of the polyprotein products gag and gag-pol into functional core proteins and essential enzymes. Proteases are required to produce a mature retrovirus (Patrick *et al*., 1996). Protease inhibitors competitively bind to the protease substrate site, resulting in the production of immature, non-infectious particles (Lewis *et al*., 1997). These class of drugs include: Nelfinavir, (NFV), Saquinavir (SQV), Ritonavir (RTV), Indinavir (IDV), Amprenavir (APV), Lopinavir/ritonavir (LPV/RTV), Fosamprenavir (FPV), Atazanavir (ATZ), Tripranavir (TPV), Darunavir (DRV) (Valentina M. *et al.*, 2004). Nelfinavir is not boosted but intend to be reserved for use during pregnancy.

Possible contamination of Nelfinavir stock with the potential carcinogen ethyl methyl sulphonate has recently prompted the withdrawal of the drug stock and the suspension of its European marketing authorization pending the results of further toxicity (Mike *et al*., 2007).

FUSION INHIBITORS: This class of antiretroviral drugs blocks HIV from fusing with a cell membrane to enter and infect it. Fusion inhibitors block the last step in the three-step viral entry process consisting of attachment, co-receptor binding and fusion, thereby preventing viral capsid entry into the host cell (Michael *et al*., 2004). Fusion inhibitors exploit the gp41 conformational transition that follows gp120-CD4 binding and co-receptor binding, and precedes pore formation. A fundamental step in the fusion process involves the interaction between the two different peptide (HR1 (heptad repeat 1) and HR2 (heptad repeat 2)) that make up the six- helix bundle, and fusion inhibitor development has tended to concentrate on molecules that act as peptide mimics, blocking the interactions that are necessary for entry e.g. Enfuvirtide

INTEGRASE INHIBITORS: They inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell. There are several integrase inhibitors currently under clinical trial and Raltegravir became the first to receive FDA approval in October, 2007.

ENTRY INHIBITORS: They block HIV from the host cell by binding CCR5, a molecule on the viral membrane termed a co-receptor that HIV normally uses for entry into the cell (Veronica *et al.*, 2006).

MATURATION INHIBITORS: They inhibit the last step in gag processing in which the viral capsid polyprotein is cleaved, thereby blocking the conversion of the polyprotein into the mature capsid protein (p24). Because these viral particles have a defensive core, the virions released consist mainly of non-infectious particles. Although two are under investigation, Bevirimat (panacos pharmaceuticals, 2007) and Vivecon.

INITIATION OF ANTIRETROVIRAL THERAPY IN HIV/AIDS CLINICAL MANAGEMENT

There is strong evidence supporting the use of the CD4 T-cell count as the major determinant in initiating therapy (Hogg *et al.*, 2001), (Yeni *et al*., 2004). The plasma HIV RNA level remains an independent predictor of clinical outcome in patients who do not receive ART and is the best available guide for monitoring the effectiveness of ART. The plasma HIV RNA level has been shown to be the strongest predictor of progression to AIDS, with a continuum of risk and no lower-limit threshold. Plasma HIV RNA levels indicate the magnitude of HIV replication, while CD4 cell counts indicate the extent of immune damage already suffered (Yeni *et al.*, 2004). Measurements of plasma HIV RNA level and CD4 cells should therefore guide the initiation of antiretroviral therapy (although the exact timing remains a debatable issue).

The durability of virologic success can be predicted by the extent of RNA suppression: the lower the plasma HIV RNA level, the longer the duration of response. A plasma HIV RNA level below 400 to 500 copies/ml was until recently considered a reasonable therapeutic goal (Mellors *et al*., 1997). The time needed to achieve maximal

virologic response (i.e. to reach undetectable plasma levels) under a given therapeutic regimen is related to baseline HIV RNA levels, the potency of the combination and the sensitivity of the assay. Studies have shown that the plasma HIV RNA level is usually reached after 20 weeks of treatment, although sometimes not until 24 to 28 weeks, particularly if an ultra sensitive assay is used and or the patient's baseline level was high (Hogg *et al*., 2001).

ANTIRETROVIRAL DRUGS TREATMENT GUIDELINES

Antiretroviral drug treatment guidelines have changed many times. Early recommendations attempted a "hit hard, hit early" approach. It is a more conservative approach followed with a starting point somewhere between 350 and 500 CD4+ T-cells/mm^3. The current guidelines use new criteria to consider starting HAART, as described below. However, there remain a range of views on this subject and the decision of whether to commence treatment ultimately rests with the patient and their doctor.

The current guidelines for antiretroviral therapy (ART) from the World Health Organizations reflect the 2003 changes to the guidelines and recommend that in resource-limited settings (that is, developing nations), HIV infected adults and adolescents should start ART when HIV infection has been confirmed and one of the following conditions is present (WHO, 2003): clinically advanced HIV disease, WHO stage IV HIV disease, irrespective of the CD4 cell count, WHO stage III disease with consideration of using CD4 cell counts less than 350/µl to assist decision making and WHO stage I or II HIV disease with CD4 cell counts less than 200/µl. The treatment guidelines in the USA are set by the United States Department of Health and Human Services (DHHS). The current guidelines for adults and adolescents were stated on October 6, 2005 (panel on clinical practice for HIV infection, 2005): All patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4+ T-cell count should receive Antiretroviral therapy (ART). ART is also recommended for asymptomatic patients with less than 200 CD4+ T-cells/µl.

Asymptomatic patients with CD4+ T-cell counts of 201-350 cells/µl should be offered treatment. For asymptomatic patients with CD4+ T-cell of greater than 350 cells/µl and plasma HIV RNA greater than 100,000 copies/nil, most experienced clinicians defer therapy but some clinicians may consider initiating treatment.

Therapy should be deferred for patients with CD4+ T-cells counts of greater than 350 cells/µl andn plasma HIV RNA less than 100,000 copies/ml. The preferred initial regimens (DHHS, 2005) are as follows:

- Efavirenz + Zidovudine + Lamivudine
- Efavirenz + Tenofovir + Emtricitabine
- Lopinavir boosted with Ritonavir + Zidovudine + Lamivudine
- Lopinavir boosted with Ritonavir + Tenofovir + Emtricitabine

In countries with a high rate of baseline resistance, resistance testing is recommended prior to starting treatment, or if the initiation of treatment is urgent, then a "best guess" treatment regimen should be started which is then modified on the basis of resistance testing. In the UK, there is 11.8% medium to high level resistance at baseline to the combination of Zidovudine + Lamivudine + Efavirenz and 6.4% medium to high level resistance to Stavudine + Lamivudine + Nevirapine (UK group of transmitted HIV drug resistance, 2005) (Gazzard *et al*., 2005).

HIV disease progression in children is more rapid than in adults, and laboratory parameters are less predictive of risk for disease progression, particularly for young infants, treatment recommendations from the DHHS have been more aggressive in children than in adults. In 2005, the Centers for Disease Control and Prevention in the United States recommended a 28-day HIV drug regimen for those who have been exposed to HIV (HIV Post Exposure Prophylaxis (PEP) (Smith D *et al*., 2005). The drugs have demonstrated effectiveness in preventing the virus nearly 100% of the time in those who received the treatment within the initial 24 hours of exposure. The effectiveness falls to 52% of the time in those who are treated within 72 hours. Those not treated within the first 72 hours are not recommended candidates for the regimen.

EFFICACY OF HAART AGAINST HIV

Infection with Human Immunodeficiency Virus (HIV) is treated with combinations of drugs from a set of antiretroviral agents. Each of these drugs targets one of the two viral enzymes, Protease (PRO) or Reverse

Transcriptase (RT) and these classes; like Protease Inhibitors (PI) binding to the protease active sites, nucleoside RT inhibitors (NRTI) acting as chain terminating substrates during reverse transcription and non-nucleoside RT inhibitors (NNRTI) that directly bind to the RT molecule, fusion inhibitors (FI) that block viral cell entry by targeting the HIV envelope protein gp41. Despite the introduction of highly active antiretroviral therapy (HAART), as combination therapy consisting of three to six different inhibitors from at least two different drug classes, it is still impossible to eradicate the virus from the patients' bodies (DHHS, 2004). Therefore, current treatment strategies aim at maximal suppression of virus load levels (the number of free virus particles in the blood plasma) over long periods. Aside from inducing strong side effects, the long term effectiveness of HAART is also limited by the evolution of drug-resistant variants. Even in patients with viral load level suppressed below detectable limits (500 copies/ml), ongoing viral replication can be found in a variety of tissues and cell types. Persistent virus production is further facilitated by sub-inhibitory drug levels in infected cells or by host immune failure. Therefore, pre-existing or newly produced drug resistant mutants can emerge that have a selective advantage under drug pressure. These escape mutants become dominant in the virus population and lead to viral rebound and therapy failure.

The genetic basis of drug resistance of HIV high mutation rate is due to lack of a proof-reading mechanism together with its high replication rate. Many polymorphisms in the viral genome have been linked to drug resistance. The life cycle of HIV can be as short about 1.5 days: from viral entry into a cell: through replication, assembly, and release of additional viruses to infection of other cells (Perelson *et al*., 1997).

HIV lacks proof reading enzymes to correct errors made when it converts its RNA into DNA via reverse transcription. Its short life cycle and high error rate causes the virus to mutate very rapidly, resulting in a high genetic variability of HIV. 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 defences such as the human immune system, and antiretrovitral drugs.

The more active the copies of the virus the greatest the possibility that one resistant to antiretroviral drugs will be made, so antiretroviral combination therapy defends against resistance by suppressing HIV replication as much as possible (AIDS Education, 2005). Combinations of antiretroviral drugs create multiple obstacles to HIV replication to keep their number of off-springs low and reduce the possibility of a superior mutation. If a mutation arises that convey resistance to one of the drugs being taken, the other drugs continue to suppress reproduction of that mutation. With rare exceptions, no individual antiretroviral drug has been demonstrated to suppress an HIV infection for long; these agents must be taken in combinations in order to have a lasting effect.

As a result, the standard of care is to use combinations of antiretroviral drugs. Combinations usually comprise two nucleoside-analogue RTIs and one non-nucleoside-analogue RTI or protease inhibitor. Combinations of antiretroviral drugs are subject to positive and negative synergy which limits the number of useful combinations. For example, ddl and AZT inhibit each other, so taking then together is less effective than taking either one separately (DHHS, 2004).

In recent years, work has to be done to combine these complex regimens into simpler formulas termed fixed dose combinations.

For instance, two pills containing two or three medications each can be taken twice daily. This greatly increases the ease with which they can be taken, which in turn increases adherence and their effectiveness over long term. Lack of adherence is a primary cause of resistance development in medication (Hirsch *et al*., 2008).

The highly mutagenic nature of HIV demands 98% adherence to drug cocktails for the drugs to be totally effective (that means missing less than 6 doses per year). Patient's ability to adhere and to maintain one regimen will not develop resistance. This will greatly increase chances of long-term survival. HIV treatment should reduce viral load to the point at which it is undetectable. An undetectable viral load does not mean that the HIV infection is gone. It simply means that the test is not sensitive enough to detect the small amount of HIV left on the blood. Successful HIV treatment can lower viral load, which may reduce the risk of HIV transmission (DHHS, 2004).

MONITORING OF ANTIRETROVIRAL DRUGS USED IN HIV/AIDS CLINICAL MANAGEMENT

In monitoring the progress of HAART, various tests are conducted between 3-6 months after the initiation of therapy with the drugs.

For effective treatment, the drugs used should have less adverse effect on the patient. It should be able to suppress the viral replication and increase the CD4 cells. Some of the tests which are conducted are plasma viral load, CD4 count, Full Blood Examination (FBE), liver function test, electrolytes test, renal function test, amylase and lipase test. Patients on therapy should have CD4 count and plasma viral load monitored at regular intervals.

On effective therapy, plasma viral load falls rapidly as viral replication is inhibited (Gottlied *et al*, 2002). By 3-6months, a fall to <50 copies/ml should be expected.

Factors affecting HAART includes patient's willingness to start therapy, to know effective regimen combination to therapy, drug side effect, pill burden and dosage schedule, drug-drug interactions and environmental factors.

RESISTANCE TO ANTIRETROVIRAL DRUGS USED IN HIV/AIDS CLINICAL MANAGEMENT

Drug resistance remains a major obstacle to the ability of antiretroviral drugs to delay disease progression.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS RESISTANCE

HIV NRTI resistance results from base changes within the RT enzyme, provoking amino acid substitutions in the transcribed enzyme, which in turn confer structural changes at the enzyme active site or at associated functional areas. Each NRTI induces a predictable set of genetic alterations in a step-wise fashion. Primary mutations generally arise first, with secondary mutations developing during continued therapy (Loveday, 2001).

Data from modified HIV-2 mutants show that HIV-2 RT resistance can be conferred by mutations at sites homologous to these for HIV-1 RT NRTI resistance. In a cell free system, site directed mutagenesis of HIV-2 RT amino acid residues homologous to residues in HIV-1 reduces the sensitivity of mutated HIV-2 to NRTIs. The HIV-1 RT mutation T215Y confers resistance to zidovudine. Based on further analysis of HIV-2 mutants; it appears that the homologue S215Y mutant in HIV-2 RT confers similar resistance to zidovudine by repositioning the template-primer (Perach *et al.*, 1997).

PROTEASE INHIBITOR RESISTANCE

PI resistance to HIV-1 is not completely understood. Mutations that confer drug resistance have been identified in protease genes. Mutations of the HIV-1 protease gene that confer resistance to specific protease inhibitors include L90M induced by saquinavir, M461 and V82A/P induced by ritonavir and D30N induced by Nelfinavir.(Temesgen *et al*, 1999).

As mentioned previously, the HIV-2 protease active site differs at 82 (Val-ile) which may confer natural HIV-2 resistance to ritonavir and indinavir (Smith N *et al.*, 2001).

ADVERSE EFFECT OF ANTIRETROVIRAL DRUGS USED IN HIV/AIDS CLINICAL MANAGEMENT

Adverse effect of antiretroviral drugs vary by drug, by ethnicity, and by individual and by interaction with other drugs, including alcohol. Hypersensivity to some drugs may occur in some individuals (Lan Mc Nicholl, 2005).

Antiretroviral therapy can have a wide range of adverse effects on the human body. Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy (Carr A. et al, 2000).

Other common nuisance adverse effects are fatigue and headache caused by AZT and nightmares associated with EFV. Several uncommon but more serious adverse effects associated with antiretroviral therapy including AZT associated anaemia, d4T-associated peripheral neuropathy, PI-associated retinoid toxicity (exemplified by pruritus and ingrown toe nails) and NNRTI-associated hypersensitivity reactions, are treated according to accepted therapy for these conditions in patients not receiving HAART. However, the subtle and serious nature of other adverse effects-lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia, fat malnutrition, hyperlipidemia, bleeding disorders, osteoporosis and skin rash (Valentina et al, 2004).

In nucleoside reverse transcriptase inhibitors (NRTIS) which include Zidovudine (AZT), Lamivudine (3TC), Didanosine (ddl), Zalcitabine (ddc) and Stavudine (d4T), adverse effect of Zidovudine are nausea, headache, rash, anaemia and elevation of lactic acid levels.

Adverse effects of Lamuvidine is Neutropenia (rare). Adverse effect of Didanosine (ddl) are GI intolerance, pencreation, gout and reversible peripheral neuropathy.

Adverse effect of Zalcitabine (ddc) includes reversible peripheral neuropathy, mouth ulcers and pancreatitis while Stavudine (d4T) adverse effects are reversible peripheral neuropathy and lactic acid elevation.

In non-nucleoside reverse transcriptase inhibitors (NNRTIs) which include Nevirapine (NVP), Efavirenz (EFV) and Delavirdine (DLV), adverse effect of Nevirapine are rash and elvation of liver enzymes level. Adverse effect of Efavirenz (EFV) is central nervous system toxicity and adverse effect of Delavirdine (DLV) is rash.

In protease inhibitors (PIs) which includes Ritovir (RTV), Amprenavir (APV), Nelfinavir (NFV) and Lipinavir/Ritonavir (LPV/RTV), adverse effects of Ritovitr are Gastrointes final (GI) upset, diarrhea, elevation of liver enzyme level and hyperglyceridemia.

Adverse effect of Amprenavir (APV) are rash and gastrointestinal upset. Adverse effect of Nelfminavir (NFV) are GI upset and mostly diarrhea while adverse effects of Lipinnavir/Ritonavir (LPV/RTV) is GI upset (Valentina et al, 2004).

CONCLUSION AND RECOMMENDATIONS

The optimum time to initiate antiretroviral therapy remains an issue of extensive debate. Immune damage is seen in nearly all HIV- infected persons. This suggested that all HIV-infected persons with detectable HIV RNA levels should be treated. However, recent data on the difficulty of HIV eradication indicate that antiretroviral therapy, once initiated, may become a lifelong commitment. Because of the limitations of current antiretroviral agents, I will suggest that deferring initiation of therapy should be considered with patients with stable early disease, high CD4 cell counts and very low or undetectable plasma HIV RNA levels. Virologic studies strongly indicates that once the decision to start has been made, therapy should be maximally suppressive, because this is the only way to limit the potential for selection of resistant variants. Two nucleoside reverse transcriptase inhibitors (NRTIs) and a Protease Inhibitor (PI) or two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) are currently recommended for initial therapy, but a number of other potent options should also be considered because some patients may need more potent regimens to achieve a complete virologic response.

A change to a salvage regimen should be strongly considered first and second line of treatment fails. The decision should be carefully considered because the number of effective regimens is still limited and any change in antiretroviral therapy increases future therapeutic constraints (many advances stage patients may have already received all the available treatments). Although some of the drugs in development may have a partially different resistant pattern with respect to existing drugs, some level of cross resistance is likely to exist between all members of the same class of presently available antiretroviral drugs. New strategies for long-term control of viral replication should be considered. Controlled trials should be investigated whether aggressive therapy may bring about better-tolerated regimen. This clearly shows that the road to less complex regimens may be long and difficult. Other strategies, such as intensification (adding agents if initial response is good but not optimal) and consolidation (adding an agent to an already successful regimen to promote durability) are under investigation. Finally, despite some limitations, potent antiretroviral combinations have clearly produced a significant reduction of disease progression, morbidity and mortality in HIV-infected individuals. New classes of antiretroviral and less burden some regimens may eventually expand treatment options and increase the long term efficacy of treatments though better tolerability and adherence profiles.

REFERENCES

1. Ademola H. Fagbami. Medical virology, lecture supplements, pp 112-116. NIHINCO Prints Ibadan.

AIDS Education Online (2005). HIV Medication. http.//aidsdrugsonline.com/ article&id/50&itemid/27html. (Retrieved on 2008).

2. *Bikandou B, Takehisa J, Mboudjeka I, Ido E, Kuwata T and Miyazaki Y (2000). Genetic subtypes of HIV type 1 in Republic of Congo. AIDS Research and Human Retroviruses: 16:613-619*

3. *Carpenter C. (1997). Antiviral therapy for HIV infection. Updated Recommendation of the International AIDS society-USA Panel. Journal of the American Medical Association, June 25, 277: 1962-1969.*

4. *Carr A and Cooper D.A (2000). Adverse effects of antiretroviral therapy. Lancet: 356: 1423-1430.*

5. *Chan DC, Fass D, Berger, JM and Kim PS, (1997). "Core Stucture of gp41 from the HIV Envelope Glycoprotein. Cell 89: 263-273 http://www.its.caltech.edu/-chanlab/pdfchancell1997.pdf.*

6. *Chen CH, Mathews, T.J, McDanal C.B et al (1995). A molecular clasp in the human immunodeficiency virus (HIV) type 1 TM protein determines the anti-HIV activity of gp41 derivatives: implication for viral fusion. Journal of Virology, 69: 3771-3777*

7. *Chen R.Y, Kilby, J.M and Saag, M.S (2002). Enfuvirtide. Expert Opinion in Investigational Drugs 11: 1837-1843.*

8. *Choe, H., Farzan, M., Sun, Y., Sullivan, N., Rollins, B., Ponath, P.D. et al. (1996). The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. Cell 85: 1135–1148.*

9. *Conclissen, M., Mulder-Kampinga, G., Veenstra, J., Zorgdrager, F., Kuiken, C and Hartman, S. (1995). Syncytiuminducing (S1) phenotype suppression at seroconversion after intramuscular inoculation of a non-syncytium-inducing/SI phenotypically mixed human immunodeficiency virus population. Journal of Virology 69, 1810-1818.*

10. *Detels T., Munoz, A., McFarlane G., Kingsley L.A., Margolick J.B., Giorgi J, et al (1998). Effectiveness of poten antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. AIDS Cohort Study Investigators. Journal of the American Medical Association, 280:1497-503.*

11. *Department of Health and Human Services (August 2006). HIV and its Treatment: What You Should Know. http://aidsinfo.nih.gov/ContentFiles/HIV andItsTreatment_cbrochure_en.pdf. (Retrieved on 4 November 2006).*

12. *Department of Human and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, 10 October, 2006. http:/aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (accessed 5 February, 2007).*

13. *Dybul M, Fauci AS, Bartlett JG. Kaplan JE, and Pau AK; Panel on Clinical Practices for Treatment of HIV 9September 2002). "Guidelines for using antiretroviral agents among HIV-infected adults and adolescents". Annual Internal Medicine. 137:381-433.*

14. *Eron J. Jr., Yeni P, and Gathe J. Jr (2006). The klean study of fosamprenavir – ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48weeks: a randomized non-inferiority trial. Lancet, 368: 476-482.*

15. *Gotlieb G.S., Sow P.S. and Hawes S.E. 92002). Equal Plasma Viral Loads Predict a Similar Rate of CD+ T Cell Decline in Human Immunodeficiency Virus (HIV) Type 1 – And HIV-2 Infected individuals from Senegal, West Africa. Infectious Diseases. 185: 905-914*

16. *Gazzard B, Bernard AJ, Boffito M et al (2006). Britain HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. HIV Medicine; 7:487-503.*

17. *Gazzard B (2005). British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with entiretroviral therapy. HIVMedical 2:1-61.*

18. *Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents (2005). http://.aidsinfo.nih.gov.*

19. *Introduction to HIV types, groups and subtypes. http://avert.org/hiv/hiv-1.html (ACCESSED 12 November, 2008)*

20. *Hirsch MS, Gunthard HF and Schapiro (2008). Clinical Infectious Diseases; 47:266-285.*

21. *HIV Sequence compendium 2008 Introduction. http://www.hiv.lanl.gov/cont/ sequence/hiv/compendium/2008/frontmatter.pdf.*

22. *Hogg R.S., Yip B., Chan K.J., Wood E, Craib K.J, O'Shaughnessy MV and Montaner JS (2001). Rates of disease progression by baseline CE4 cell count and viral load after initiating triple-drug therapy, Journal of the American Medical Association; 286:2568-2577.*

23. *Ian McNicholl (2005). "Adverse Events of Antiretroviral Drugs". University of California San Francisco. http:hivinsite.ucsf.edu/Insite?page=ar-05-0.*

24. *(Retrieved 7 January, 2006)*

25. *International Committee on Taxonomy of Viruses. "61. Retroviridae". National Institutes of Health. (Retrieved on 28 February, 2006).*

26. *Janssens, W., Buve, A, and Nkengasong, J.N. (1997). The puzzle of HIV-1 subtypes in Africa. AIDS; 11: 705-712.*

27. *Jawetz, Mclnick and Adelderg's (2007). Medical microbiology, 24th edn. Pp 604-618. Mc Gram Hill, printed in United State of America.*

28. *Jeeninga, R.E., Hoogenkamp, M., Arman-Ugon, M., de Baar, M. Verhoef, K. and Berkhout, B. (2002). Functional differences between the long terminal repeat transcriptional promoters of human Immunodeficiency virus type 1 subtype A through G. Journal of Virology 74, 3740-3751.*

29. *Joint United Nations Programme on HIV/AIDS (UNAIDS) – WHO (1997). Revised recommendations for the selection and use of HIV antibody tests. Weekly epidemiology Record; 72:81-87.*

30. *Junghans C., Ledergerber B., Chan P., Weber R, and Egger M (1999). Sex differences in HIV-1 viral load and progressive to AIDS. Swiss HIV Cohort Study. Lancet; 353:589.*

31. *Kallas E., Caruso S, and Lopez D,, (2002). First identification of human immunodeficiency virus type 2 (HIV-2) transmission in Brazil, Submitted for publication.*

32. *Kato K., H. and Takebe Y. (1999). Role of naturally occurring basic amino acid substituations in the human immunodeficiency virus type 1 subtype E evelope V3 loop on viral coreceptor usage and cell tropism. Journal of Virology 73:5520-6.*

33. *Katzenstein D et al (1996). The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. New England Journal of Medicine, 335: 1091-1098.*

34. *Kilby, J.M. and Eron, J.J., (2003). Novel therapies based on mechanisms of HIV-1 cell entry. New England Journal of Medicine 348:2228:38*

35. *Kilger, Y., Gallo, S.A., and Peisajovich, S.G. (2001). Mode of action of an antiviral peptide from HIV-1. Inhibition at a post-lipid mixing stage. Journal of Biological Chemistry 276: 187-214.*

36. *Loemba, H., Brenner, B., Parmiak, M.A., Ma'ayan, S., Spira, B. and Moisi, D. (2002). Co-receptor usage and HIV-1 inter-clade C polymorphisms in the protease and reverse transcriptase genes of HIV-1 isolates from Ethiopia and Botswana. Antiviral Therapy, 7:141-148.*

37. *Loveday C. (2001). International perspectives on antiretroviral resistance. Nucleoside reverse transcriptase inhibitor resistance. Journal Acquire Immune Deficiency Symdrome; 26 Supplement 1: S10-24.*

38. *Maia Hightower and Esper Georges Kallas (2003). Diagnosis, Antiretroviral Therapy, and Emergence of Resistance to Antiretroviral Agent in HIV-2 infection. Brazilian Journal of Infectious Diseases; 7:7-15.*

39. *Martin J.A., Mobberley M.A. and Redstraw S. (1991). The inhibitory activity of a peptide derivative against the growth of simian immunodeficiency virus in C8166 cells. Biochemical Biophysics Response Communication; 176:180-8.*

40. *Mellors J.W. Munoz. A., Giogi J.V and Margolick J.B. (1997). Plasma viral load and CD4+lymphocytes as prognostic markers of HIV-1 infection. Annual Internal Medicine; 126:946-54.*

41. *Micheal L., Greenbery and nick Cammack (2004). Journal of antimicrobial Chemotherapy; 54: 333-340.*

42. *Mike Y., Staszweski S. and Clotet B. (2007). Overview of boosted protease inhibitors in treatment-experienced HIV-infected patients. Journal of Antimicrobial Chemotherapy; 60: 1195-1205.*

43. *Montano M.A., Novitsky V.A., Blackard J.T., Cho N.L. Katzenstein D.A. and Essex M. (1997). Divergent transcriptional regulation among expanding human immunodeficiency virus type 1 subtypes. Journal of Virology 71, 8657-65*

44. *Montessori V., Press N. and Harries M. (2004). Adverse effect of antiretroviral therapy. Candian Medical Association Journal 170, 229-28.*

45. *Nigeria Business Coalition against AIDS (NIBUCCA), 2008*

46. *http//nibucca.org (accessed May, 2008)*

47. *O'Brian T., George J and Epstein J. (1992). Recommendation and reports: Testing for antibodies to human Immune deficiency virus type 2 in the United States. Morbility Mortality Weekly Report 41:1-9*

48. *Panacos Pharmaceuticals. Clinical Trial: Phase 2 safety and Efficacy Study of Bevirimat Functional Monotheraphy in HIV Treatment- Experienced Patients for 2 weeks. Clinical Trials.gov. http://clinicaltrials.gov/ct/shows/ NCT00511368. (Retrieved on August 9, 2007)*

49. *Panel on Clinical Practices for Treatment of HIV infections (October 6, 2005). "Guidelines for the use of Antiretroval Agents in HIV-1- Infected Adults and Adolesents". http://aidsinfo.nif.gov/Contentsfiles/AdultandAdolescentGL.pdf. (Retrieved on January 17, 2006)*

50. *Patrick A.K., Mo H and Markowitz M (1996). Antiviral and resistance studies of AG1343, an orally bioavailable inhibitor of human innunodeficiency virus protease. Antimicrobial Agents Chemotheraphy; 40: 292-7.*

51. *Perelson A. (1997). Decay characteristics of HIV-1-infected compartments during combination therapy. Nature 387; 188-191.*

52. *Perach M., Rubinek T., Hughes S.H. and Hizi A (1997). Analysis of HIV @ RT mutants provides evidence that resistance of HIV-1 RT and HIV-2 RT to nucleoside analogs involves a repositioning of the template- primer. Journal of molecular Biology; 268:648-54.*

53. *Philips AN, Staszewaki S, Weber R and Kirk O.. (2001). HIV viral load response to antiretroviral theraphy according to the baseline CD4 cell count and viral load. Journal of the American Medical Association; 288:2560-7.*

54. *Pieniazek D., Ellenberger D. and Jainini L.M.. (1999) Predominance of human immunedeficiency virus type 2 subtype B in Abidjan, Ivory Coast. AIDS research and Human Retroviruses 15:603-8.*

55. *Piot, P. and Bartos M. (2002). The epidemiology of HIV and AIDS. In AIDS in Africa, 2nd edition. pp. 200-17. Kluwer Academic/ Plenum Publishers, New York, NY, USA*

56. *Shalom Spira and Mark A., Hugues L., Dan T. and Bluma G.B (2003). Impact of clade dicersity onb HIV-1 virulence, antiretroviral drug sensitivity and drug resistance. Journal of Antimicrobial Chemotherapy 5:229-240.*

57. *Shiino, T., Kato, K., Kodaka, N., Miyakuni, T., Takebe, Y. and Sato, H. (2000). A group of V3 sequences from immunodeficiency virus type 1 subtype E non- syncytium inducing, CCR5- using variants are resistant to positive selection pressure. Journal of Virology 74:1069- 1078.*

58. *Smith, Johanna A; Daniel, Rene (2006). Division of Infectious Diseass, center for Human Virology, Thomas Jefferson University, Philadelphia. Following the path of the virus: the exploitation of host DNA repair mechanisms by retroviruses. ACS Chemical Biology 1 (4): 217-226.*

59. *Smith D.K, Grohskopf L.A and Black BJ, (2005). "Antiretroviral postexposure prophylaxis after sexuel, injection-drug use, or other nonoccupational exposyre to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. Morbility Mortality Weekly Reports 54:1-20*

60. *Smith N.A., Shaw T. and Berry N (2001). Antiretroviral therapy for HIV-2 infected patients. Journal of infectious diseases 42:126-133*

61. *Temesgen Z. and Wright A.J (1999). Antiretroval. Mayo clinical procedure 74:1284-301.*

62. *United kingdom group of Transmitted HIV Drug Resistance (2005) . Time trends in primary resistance to HIV drugs in the United Kingdom: multicenter observational study. British medical journal 331 (7529): 1368-1371.*

63. *United states Department of Health and Human Services.*

64. *http://hrsa.gov/hab/?CGchap5.pdf. (Retrieved July 2006).*

65. *Valentine. M and Natasha. P (2004). Adverse effects of antiretroviral therapy for HIV infection. Canadian medical Association Journal 170:229-238.*

66. *Veronica. B., Eva.P. and Vincent.S. (2006). HIV entry inhibitors: mechanisms of action and resistance pathways. Journal of Antimicrobial Chemotherapy 57(4):619-627.*

67. *Worgall, S., Connor, R., Kaner, R. J., Fenamore, E., Sheridan, K.and Singh R. (1999). Expression and use of human immunodeficiency virus type 1 Goreceptors by human alveolar macrophages. Journal of Virology 73:5865-5874.*

68. *Wild, C., Greenwell, T. and Matthews, T. (1993). A synthetic peptide from HIV-1 gp41 is a potent inhibitor of virus- mediated cell-cell fusion. AIDS research and Human Retroviruses 9:1051-1053.*

69. *Wild C.T., Shugars, D.C and Greenwell, T. K. (1994). Pepsides corresponding to a predictive alpha-helical domain of human immunedeficiency virus type 1 gp41 are potent inhibitors of virus infection. Proceedings of the National Academy of sciences. USA. 91: 9770-9774.*

70. *World Health Organization (2003). Scaling up retroviral therapy in resource limited settings http://www.who.int/hiv/pub/prevcare/en/arreversion 2003en.pdf. Retrieved on January 17, 2006)*

71. *Yeni P.G., Hammer S.M and Hirsch M.S. (2004). Treatment for adult HIV: recommendations of the international AIDS society- USA panel. Journal of the American medical Association; 292:251-65.*