ASSESSMENT OF RATIONAL USE OF ANTIRETROVIRAL DRUGS IN HEALTH INSTITUTIONS IN KANO METROPOLIS

BY

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DECLARATION

I declare that the work in the dissertation entitled 'Assessment of rational use of antiretroviral drugs in Health institutions in Kano metropolis has been performed by me in the Department of Pharmacology and Clinical Pharmacy under the supervision of Prof. I. A. Aguye and Dr J. A. Anuka

The information derived from the literature has been duly acknowledged in the text and a list of references provided. No part of this dissertation was previously presented for another degree or diploma at any university

Samaila Idris Gaya ---------- ----------

Signature Date

CERTIFICATION

This dissertation entitled "**ASSESSMENT OF RATIONAL USE OF ANTIRETROVIRAL DRUGS IN HEALTH INSTITUTIONS IN KANO METROPOLIS"** by Samaila Idris Gaya meets the regulations governing the award of the degree of Master of Science Pharmacology of Ahmad Bello University, Zaria, and is approved for its contribution to knowledge and literary contributions.

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DEDICATION

This work is dedicated to the Late Emir of Gaya, **Alhaji Adamu Gaya** for his special interest in my early educational pursuit and for his encouraging support. May his gentle soul continues to rest in peace, amen

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All praise be to God, the Lord of the universe. To him belong the beginning and the end and everything lies with him in its totality. He gives wisdom to whom he wish to and whoever has been given wisdom has certainly been given much good.

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ABSTRACT

With the national prevalence of 5.0% in Nigeria, HIV infections have become one of the most dreadly medical challenges. Availability of highly active antiretroviral therapy (HAART) has given a new hope of living with somewhat terminal syndrome. The availability, affordability and effective usage of antiretrovirals in Kano (North West Nigeria) was studied to provide a data for compliance study with the National Standard Treatment Guideline (STG) and also for comparison with other International data. A total of 138 patients (pooled from three health institutions) were studied at random through a structured questionnaire and patient medication information record. The mean age of the patients was 35.6years with a standard deviation of 7.8 years. Antiretroviral drugs are readily available. However, affordability among the subjects studied was 97.5% and 47.5% at a subsidized federal government rate of one thousand naira per month and at a retail price of ten thousands naira per month respectively. Adherence to therapy was difficult with about 60% of the patients having missed at least a dose in their treatment schedule. In fact, 25% of them have missed at least a dose within a week preceding the study. Factors responsible for non-adherence (in decreasing order) were fasting, cumbersome (indefinite) treatment period, forgetfulness, side effects (mainly skin rash), fear of stigmatization (as patients can't take medication in others presence), unavailability and travelling. The study also showed that 88.4% of the patients were on triple HAART with 11.6% on either dual or monotherapy. Antiretroviral drugs used in the management of HIV/AIDS were drawn from the lamivudine, Zidovudine, Stavudine, and Nevirapine group.

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ABBREVIATIONS/DEFINITION OF TERMS USED

- CD4 — The T-cell surface receptor utilized by HIV in order to attach, enter and infect a cell.
- Cross – resistance — When a mutation associated with drug A leads to in vitro phenotypic resistance to drug B
- Genotypic-Resistance — A misnomer – a term used to describe the presence of genotypic change (mutation) that might confer phenotypic resistance.
- HAART — Highly active antiretroviral therapy
- HIV — The human immuno-deficiency virus that is widely recognized etiological agent of AIDS.
- Lipodystrophy — Defective metabolism of fat, which can result in fat redistribution (e.g buffalo hump)
- Maculopapular — Describes a lesion with a flat base surrounding a popule in the centre.
- NNRTI — Non-nucleoside reverse transcriptase inhibitor
- NRTI — Nucleoside reverse transcriptase inhibitor
- Nucleoside — Chemical compound comprising a purine or pyrimidine base (adenine (A), guanine (G), thymine (T), Cytosine (C) or Uracil (U) attached to a five carbon sugar – nucleoside are the building blocks of DNA and RNA (e.g thymidine)

• Phenotypic resistance	ıDecrease in the concentration of drug that is needed to inhibit the growth of the virus by 50% usually expressed as an x-fold rise to a drug in vitro.
• Protease Inhibitors (PI)	Anti HIV agent which inhibit the action of protease (an enzyme which cleaves protein into smaller fragments)
• Resistance	A change in the phenotypic susceptibility of the strain of HIV infecting the patient, resulting from alteration in the viral genotype and manifested as a loss of susceptibility to the inhibitory effects of the drug (s) in vitro . Viral resistance is used as a relative term, described more accurately as varying degrees of reduced sensitivity to a drug.
• Reverse transcriptase Inhibitors	Compound that inhibits the synthesis of DNA copy from RNA template
• Reverse transcriptase	An enzyme which can construct double strand DNA molecules from single stranded RNA templates.
• Viral load	A quantitative measure of the amount of circulating virion associated HIV RNA in the body, most commonly determined in the plasma.

CHAPTER ONE

1.0. INTRODUCTION AND LITERATURE REVIEW

When it first appeared, AIDS (clinical stage of HIV infection) was recognized only as a severe previously unseen immuno-deficiency syndrome of unknown cause. In 1981, initial reports describe the human immuno-deficiency virus (HIV) epidemic in the U.S. as a clinical syndrome of immune deficiency well before researchers identified HIV and showed it to be the cause of the syndrome (CDC, 1981; 1988).

Human immuno-deficiency virus infection initially only recognized among homosexuals in the U.S. in 1981 resulted in an early hypothesis that AIDS resulted from a behaviour specific to gay men because at that time in 1980s, gay men sometimes inhale amyl and butyl nitrate to enhance sexual performance. This was however dismissed when the syndrome was later observed in other population group in Europe, America and Central Africa. The observation of symptoms among heterosexuals, bisexuals, homosexuals, hemophilics, intravenous drug users and in babies of infected mothers led to the inference that HIV was an infection process. In 1983, HIV was isolated and was later termed HIV-1 after the discovery of HIV-2 in West African region in 1986 (CDC1988).

Recent advances in basic and clinical research in HIV disease have dramatically changed the perspective of patients, clinicians and researchers allowing them to view HIV infection as a potentially treatable and conceivably curable disease rather than one that is relentlessly progressive and inevitably fatal (Cohen, 1993).

Untreated HIV disease is a chronic progressive process that begins with infection and is often followed by a primary HIV syndrome and progresses in adults over a median period of more than ten years to a late stage AIDS.

1.1 EPIDEMIOLOGY OF HIV INFECTION

HIV infection/AIDS is truly a global pandemic with case reported from every continent. The reported cases of AIDS worldwide are grossly an underestimate of true incidence, mostly because of the incomplete reporting mechanisms in certain developing countries.

As at end of 2001, the joint United Nation Programme on HIV/AIDS estimated the number of people infected with HIV across the globe at 40 million of whom 17.6 million (47%) were women 15 to 49 years old and 2.7 million were children under 15 years (UNAIDS, 2003).

Although the sub-Saharan Africa has only 10% of the world's population, 70% of HIV infected persons in the world are found there (UNAIDS, 2003). This finding has been attributed to the factors that enhance the transmission of the disease, which are prevalent in Africa. These include multiple sex partners/commercial sex workers, other sexually transmitted diseases, poverty, high level of illiteracy, poor healthcare delivery system and rigid attachment to traditional beliefs.

Nigeria has not been spared by the HIV/AIDS pandemic. Presently Nigeria ranks fourth after India, South Africa and Ethiopia on the list of the worst affected countries worldwide (HIV fact sheet 2002).

Since 1986 when the first case was reported in Nigeria, the disease has since grown to epidemic level with rapidly increasing prevalence rate of 1.8% in 1993, 3.8% in 1994, 4.5% in 1996, 5.4% in 1999, 5.8% in 2001 and 5.0% in 2003 based on HIV/Syphilis sero- prevalence sentinel surveys among women attending antenatal clinic. Although some parts of the country are more affected than others, all states record more than 1% prevalence. In 2003, prevalence rate range from 1.2% in Osun State to 12% in Cross River State. National prevalence is higher in urban than rural populations.

About 10% of every dying AIDS patient in the world is a Nigerian while one in every thirteenth world daily-infected person is a Nigeria (Sentinel report 2003). The higher prevalence is in the age group 19-25 years. These are productive, reproductive and economically viable segment of the society (population bureau 2002).

1.2 DISEASE TRANSMISSION AND AETIOLOGY

Human immuno-deficiency virus (HIV) is found in bodily fluids including, blood, semen, vaginal fluids and breast milk and can be transmitted from infected individuals to others through four different ways.

a. Sexual transmission (vaginal, oral and anal) contributes to about 80-85% of transmission and is the main mode of transmission in Nigeria and other parts of Saharan Africa. While the probability of transmitting HIV infection in a single act is very low, several factors increase the risk of the infection. These factors include presence of sexually transmitted disease (STD), type of sexual practice(most infection occurs though vaginal intercourse though evidence exist as to the increase risk of

infection from receptive anal sex) having multiple sexual partners and women's vulnerability (population bureau 2002).

b. Through infected blood and needles. Transmission through infected blood accounts for about 5% of HIV infection. Transmission occurs through the transfusion of contaminated blood or blood products, contaminated injecting equipment, the exchange and re-use of needles, contaminated syringe and surgical operations.

c. Mother to child transmission. A mother can transmit HIV infection during pregnancy, delivery or through breast-feeding. The risk of mother to child transmission of HIV infection varies from one country to another but generally estimated to be between 15%-40%.

d. occupational exposure. Transmission by occupational exposure has been widely studied (NIMR 2003). Percutaneous, mucous membrane and cutaneous exposure to contaminated body fluids would be ready source of viral exposure in many health care settings. Studies indicate an average risk of HIV-1 sero-conversion after needle stick injury as approximately 0.3%. Post exposure prophylaxis with antiretroviral drugs significantly reduces the risk of transmission by this route.

1.3 PATHOGENESIS, CLINICAL MANIFESTATION & CLASSIFICATION

1.3.1 Pathogenesis

The hallmark of HIV disease is a profound immuno-deficiency resulting, primarily from a progressive quantitative and qualitative deficiency of the CD_4+ su**b**sets of T-lymphocytes referred to as the helper or inducer T-cells. This subset of T-cells is defined

phenotypically by the presence on its surface of a CD_4 molecule, which is the cellular receptor of HIV (Harrison 1997). Although the CD_4 T-cell is the predominant cell type that is actually infected with HIV, virtually any human cell that expresses CD_4 molecule (CD_4^+) is capable of binding to and becoming infected with HIV.

Though a number of mechanism responsible for cytopathicity and immune dysfunction of CD_4+ T-cells have been demonstrated *in vitro*, it is still unclear which mechanism is primarily responsible for the progressive depletion and functional impairment of these cells *in vivo*. Nonetheless, when the CD_4 + T-cells decline beneath a certain level, the patient is at risk of developing a variety of opportunistic diseases, particularly infection and neoplasm which are AIDS defining illness. The mechanism of immuno-suppression has been summarized to be through the following (Akanmu, 2002).

i Loss of CD_4 + T lymphocytes

ii Dysfunction of monocytes

iii Dysfunction of Cytotoxic T-cells

iv Dysfunction of T-suppressor cells

v Dysfunction of T-Natural killer cells

vi Dysfunction of B-lymphocytes

Only 30-70% of HIV-1 is associated with acute clinical symptoms ranging from mild viral syndrome to severe systemic illness. The incubation period from initial infection to onset of symptoms is an average of 21.4 days. The initial symptoms resolve within 1-2 weeks. HIV viral load in the blood peaks in the first 15-30 days concurrently with a drop

in $CD+_4$ T-cells and an increase I $CD+_8$ T-Lymphocytes. Sero –conversion occurs in 14-21 days after onset of symptoms together with symptomatic period. This time frame is in the order of 4-6 weeks (window period). During the window period, symptoms subsides and the patient enters a clinical latency period which has a varied period with a median time range being 7-10 years (NIMR 2003)

1.3.2 Clinical Manifestation

The clinical manifestations of HIV/AIDS are numerous involving organ systems and both infectious and neoplastic disease processes characteristic of severe immune depression (CDC, 1982). Patient present with a varied clinical manifestations, many of which are described in the WHO major and minor criteria for clinical definition of AIDS (in the absence of a known cause of immunosuppression).

Major criteria

a. Significant loss of weight (more than 10%)
b. Chronic diarrhoea lasting more than a month, at least 2 loose stools per day.
c. Persistent pyrexia with temperature more than 38.5^0c continuously or intermittently for more than one month.

Minor criteria

a. Generalized lymphadenopathy
b. Chronic cough for more than a month.
c. Pulmonary Tuberculosis
d. Generalized Pruritic dermatitis
e. Herpes simplex infection
f. Genital Ulcers
g. Oropharyngeal/recurrent vaginal candidiasis
h. Peripheral neuropathy
i. AIDS defining illness (kaposis sarcoma, Non Hodgkin's lymphoma, cervical cancers) etc.

In a study carried out by Akolo and his coworkers (2005) on the spectrum of clinical diseases at presentation in HIV/AIDS patients, tuberculosis was the commonest disease and was diagnosed in 41.0% of the subjects. Out of these, 33.5% had only pulmonary TB while 7.5% had disseminated TB involving meninges, lymph node, abdomen and spine. Other diseases diagnosed were diarrhoeal disease (8.5%), wasting disease (6.0%), oral candidiasis (5.0%), generalized lymphadenopathy (4.0%) and kaposis sarcoma (2.5%). Bacterial pneumonia, cryptococcal meningitis and herpes zoster were each diagnosed in (2.0%) of the subjects.

Since HIV disease is manifested in various stages, the disease presentations can be empirically divided on the degree of immuno suppressions.

1.3.3 **Classification of HIV Infections**

The revised (CDC 1993) center for disease control classification system combines three categories of the CD_4+ count with three symptoms categories and is closer to a staging system but is still described as such. The CDC, however proposed that it be used to guide clinical and therapeutic action in the management of HIV infected adolescents and adults.

The definition of the three CD_4+ T lymphocytes categories are

i. Category 1: more than 500 cell/mm^3 (or CD_4%>28%)

ii. Category 2: 200 – 499 cells/mm^3 (or CD_4% 14% - 28%)

iii. Category 3: Less than 200 cells/mm^3 (or CD_4% <14%)

And the three categories of clinical conditions used are as follows:

i. **Category A**: This category consists of one or more of the conditions listed below in an adolescent or adult (more than13 years) with documented HIV infection. Conditions listed in category B and C must not occur.

a. Asymptomatic HIV infection.
b. Persistent generalized lymphadenopathy.
c. Acute (primary) HIV infection with accompanying illness or history of acute HIV infection.

ii. **Category B**: This consists of symptomatic conditions in HIV infected adolescents or adults not included among conditions listed in clinical category C and which meets at least one of the following criteria:

a. Conditions attributed to HIV infection

b. Conditions considered by physicians to have a clinical course or to require management that is complicated by HIV infection e.g Bacillary angiomatosis, candidiasis (oropharyngeal, vulvo- vaginal poorly responsive to therapy), cervical dysplasia, constitutional symptoms such as fever (more than 38.5^0C) or diarrhea lasting greater than one month, oral hairy leukoplakia (OHL),Herpes zoster, Pelvic Inflammatory Disease (PID) particularly complicated by tubo-ovarian abscess, Peripheral neuropathy

iii. **Category C:** This includes the clinical conditions listed in 1993 AIDS surveillance case definition of the centre for disease control. The 1993 CDC AIDS case definition added a CD_4 + lymphocyte count below 200 cells/mm^3 in an active HIV positive person to the AIDS definition to sidestep the deficiencies of a definition based solely on diagnostic list. Three clinical conditions in HIV positive were also added. These are pulmonary tuberculosis, two occurrences of bacterial pneumonia within a 12-month period and in women, invasive cervical cancer.

1.3.4 **WHO Clinical Staging System for HIV Infections and Disease**

Stage 1: Asymptomatic or lymphadenopathy

Stage 2: Weight loss less than 10%, Herpes zoster, recurrent minor illness

Actively scale: Normal

Stage 3: Weight loss more than 10%, fever or diarrhea lasting more than a month, oral candidiasis, pulmonary TB in last year and severe bacterial infection.

Activity scale – in bed less than 50% of days in last month

Stage 4: HIV wasting syndrome, non-typhoid salmonella septicemia, wide range of opportunistic infections including pneumocystic carinii pneumonia, toxoplasmosis of the brain, cytomegalovirus disease, herpes simplex, disseminated endemic mycosis.

Activity scale: in bed more than 50% of days in last month.

1.4 DIAGNOSIS

Identification and isolation of human immuno-deficiency virus (HIV) enabled researchers to develop a technique for culturing from specimen, to quickly derive a relatively convenient and cost effective assay that detect antibody to HIV in the plasma of infected person (CDC, 1984). In 1984 and 1985, a reliable, sensitive and specific test for HIV infection became available and made possible to screen blood products, detect HIV infection, identify sero-conversion and construct a perspective studies to describe the course of HIV disease in asymptomatic person with serological evidence of HIV infection. The tests used in making diagnosis of HIV include:

a. ELISA (Enzyme linked immunosorbent assay). This is the commonly administered screening test for HIV infection with 99.5% accuracy.
b. Western Blot – commonly used confirmatory test with 99.9% accuracy.
c. Home test kit - This also employ the technique of ELISA with 99.8% accuracy.

Other tests less commonly employed are direct cultivation of HIV from a plasma and Polymerase chain reaction (using both DNA or RNA).

Facilities are often not readily available for laboratory diagnosis in developing countries. Therefore, the WHO clinical case definition of AIDS in Africa may be employed using at least 2 major and 2 minor criteria in the absence of known cause of immuno-suppression.

1.5 TREATMENT/MANAGEMENT OF HIV/AIDS

The therapeutic management of HIV and AIDS has evolved both rapidly and dramatically since the initial outbreak of the epidemic. Faced with a mysterious and alarming new disease that was claiming the lives of thousands of previously healthy individuals, clinicians and research scientist battled to understand the etiology of the disease and identify ways to tackle its devastating effects (Goodman and Gilman 1996).

With the development of potent antiretroviral therapy in 1996, the quality of life of HIV infected individuals has dramatically improved and the development of AIDS and death has been diverted at least for a period of time, in many individuals, even those with advanced disease by targeting the root cause of the acquired immuno-deficiency syndrome. Although, the treatments are not curative and present new challenges with respect to adverse effects and drug resistance, the modern antiretroviral therapy has resulted in a significant reduction in the morbidity and mortality of HIV disease particularly in the western world (Patella *et al* 2003).

1.5.1 Goals of Therapy

Eradication of HIV infection cannot be achieved with the available antiretroviral regimen chiefly because of the pool of latently infected CD_4+ T cells which is established during the earliest stage of acute HIV infection and persist with a long half life even with

prolonged suppression of plasma viremia to less than 5 cells/mm^3 (Chun *et al*., 1997; Roberts, 2003). The primary goals of antiretroviral treatments are therefore maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life and reduction of HIV related morbidity and mortality.

According to Akamu(2003) the goal of antiretroviral therapy can be elaborately put into:

a. Virologic goals that include

i. Reduction of viral load to less than 20 cells /mm^3

ii. Halting of disease progression

iii. Prevention or reduction of resistant strain.

b. Immunologic Goals

i. Immune reconstitution (quantitative CD4+ Cells count in normal range).

ii. Qualitative immune reconstitution.

c. Therapeutic goals directed towards:

i. Rational sequencing of drugs in fashion that achieve virologic goals.

ii. Maintaining therapeutic options

iii. Treatment that is relatively free of side effects

iv. Treatment that is realistic with regards to probability of adherence.

However, the institute of Human Virology Maryland USA (2004) has summarily puts the goals of antiretroviral therapy to precisely include the following:

i. Maximizing long-term viral suppression

ii. Minimizing risk of resistance and cross-resistance

iii. Minimizing long-term toxicity

iv. Maximizing capacity of immune reconstitution

v. Optimizing overall clinical outcome

vi. Optimizing quality of life (QOL)

vii. Minimizing overall cost of care

viii. Creating synergy with long-term public efforts.

The institute has also categorized the primary goal of antiretroviral therapy in Africa to:

i. Provide antiretroviral treatment that is accessible to people living with HIV

ii. Reduce infection and prevent premature death.

iii. Evaluate treatment as part of overall prevention strategy.

iv. Prevent economic and social destabilization.

v. Develop broader commitment to improve global health.

Adoption of treatment strategies recommended in these guidelines has resulted in substantial reduction in HIV related morbidity and mortality (Moorcroft *et al*., 1998). Plasma viremia is a strong prognostic indicator of HIV disease progression (Mellor *et al*., 1996). Viral load reductions to below limits of assay detection in a treatment naïve patient usually occur within the first 16-24 weeks of therapy. Predictors of long-term virologic success include potency of antiretroviral regimen, adherence to treatment, low baseline viremia and higher base line CD4+ cell count.

Overall, the goal of antiretroviral therapy is to reduce mortality and morbidity associated with HIV infection and maintains quality of life of people living with HIV/AIDS (PLWHA) while ensuring also preventing mother to child transmission (PMTCT).

1.5.2 Starting Antiretroviral Therapy

Growing concern over the long-term side effects of antiretroviral led the British HIV association (BHIVA) and the U S Department of health and Human services to propose a new guideline on starting an antiretroviral therapy. The British HIV Association guidelines (2003) advice clinicians to consider initiating therapy when the CD4+ cell count decline to within the range of 200—350cells/mm^3 while taking into account the rate of CD4+ cell count decline and HIV-1 RNA level, and immediate initiation of therapy if CD4+ cell count has declined to 200 cell/mm^3. Conversely the U S public health services guidelines currently recommend treatment if CD4+ cell count declines below 350 cells/mm^3 or if plasma viral load is above 51000 copies/ml^3 (Guidelines 2005). An international panel recommends starting treatment above 200cell/mm^3 in asymptomatic people with a CD4+ count falling faster than 100 cells/mm^3 yearly or with a viral load above 50000 to 100,000 copies/ml (Yeni *et al*., 2002). For poor and developing countries, anyone with AIDS, or a CD4+ count below 200 cells/mm^3 or a total lymphocyte count 1,200 cells/mm^3 should be treated (Finizi *et al*., 1999).

Based on prospective observational cohort study from Barcelona, the starting point for antiretroviral treatment in a study carried out between January 97- December. 2000 using 573 patients was found out to be at CD_4+ count of 243 cells/mm^3 and HIV RNA of 4.8$\log_{10}$Copies/ml. (Chun *et al*., 1997)

A pooled analysis of 13 cohorts from Europe and North America provide the most precise information on prognosis following the initiation of treatment (Mellor *et al*., 1997). These data indicate that CD4 T-cells count is more important prognostic indicator

than viral load for those initiating therapy. In the study, the risk of progression was also greater for those with viral load more than 100,00., older patients, those infected through injecting drug use and those with a previous diagnosis of AIDS.

According to Anthony Amowoso (2003), indication for antiretrovirals is categorized based on presenting conditions of the individually infected patients as follows;

a. Chronically infected HIV patient: regardless of viral load, treatment should be initiated in the following patients:
   i. Symptomatic (AIDS, severe symptoms)
   ii. Asymptomatic (CD_4+ cells less than200 cells/mm^3)
   iii. Asymptomatic with CD_4+ cells more than 200 cells but less than 350cells/mm^3 (treatment should be offered though controversial).

b. Asymptomatic HIV patient is based on:
   i. Degree of immuno-deficiency: In fact, no proven long term mortality benefit for starting therapy with CD_4^+ more than 200 cells/mm^3
   ii. Plasma viral RNA
   iii. Downside of antiretroviral regimen (potential risk and benefit of treatment)
   iv. Willingness of patient to begin and the likelihood of adherence.

In a study carried out by Evan Wood *et al*., (2003), survival rates following the initiation of HAART have dramatically improved among patients with CD_4+ counts less than 200 cells cells/mm^3 once adjusted for conservative estimates of physician experience and adherence. Therefore the current emphasis of therapeutic guideline on initiating therapy at CD_4^+ cell count above 200 cell/mm^3 should be examined.

The optimal time for starting therapy remains unclear and opinion will continue to change as therapy improves. Patients should be individualized and adherence should be supported once treatment starts.

In summary, the decision to begin therapy for the asymptomatic patient with more than 200 cells/mm^3 CD_4+ is complex and must be made in setting of careful patient counseling and education. Factors to be considered include the potential risk associated with treatment and the risk of early or delayed therapy initiation.

According to Brian Gazzard (2003), while commenting on antiretroviral treatment *"the patients who have done best are those who lived long enough to realize that my previous advice was incorrect"*.

1.5.3 Principle Of Antiretroviral Therapy

The cornerstone of medical management of HIV infection is an antiretroviral therapy. Suppression of HIV replication is an important component in prolonging life as well as in improving quality of life with HIV infection. The challenge to a successful antiretroviral treatment is based on a careful interplay between the clinician, patient, Drug and the virus (Anthony, 2003).

The large number of available antiretroviral agent coupled with a relative paucity of clinical end point studies make the subject of antiretroviral therapy one of the most controversial in the management of HIV infected individuals.

The WHO (2003) guideline consensus on what to treat with, in HIV infection dictates the need to use 3 or 4 drug regimen known as HAART. Dual antiretroviral regimens are not recommended as they are much less effective and pose the risk of viral resistance.

Highly active antiretroviral therapy (HAART) entails the combination of 3 drugs (usually of 2 classes). These classes are

I. Nucleoside reverse transcriptase inhibitors (NRTI's)

II. Non-Nucleoside reverse transcriptase inhibitors (NNRTI's)

III. Protease inhibitors (PI's)

IV. Fusion inhibitors (more recent).

Currently available clinical combination makes use of

a. 2NRTI and 1 NNRTI that are PI sparing
b. 2NRTI and 1 PI that are NNRTI sparing
c. 3NRTI that are both PI and NNRTI sparing
d. 2NRTI + 2PI

The criteria for the choice of the individual drugs according to guidelines for the use of antiretrovirals in adults and adolescents USA (2005) are:

i. use only drugs with excellent potency profile
ii. use drugs with high mutation threshold
iii. use drugs with limited class cross-resistance
iv. use drugs with limited toxicity or side effects

In general, combination of three drugs often referred to, as triple therapy is required to achieve this goal. A double combination therapy is not desirable but might be acceptable in certain situation where the protease inhibitors or the non-nucleoside reverse transcriptase inhibitors are contra-indicated or where drug compliance is far seen as a problem.

Regimen should be simplified as much as possible by reducing the number of pills and therapy frequency and by minimizing drugs interactions and side effects (Barttlet *et al*., 2000; Cohen 2002). The panel on clinical practice for treatment of HIV infection also affirms that regimen selection should be individualized on the basis of the advantages of each regimen and the consideration of numerous other factors and that head to head randomized prospective clinical trial when available provide the best information regarding the relative performance of antiretroviral regimen.

1.5.4 Compliance/Adherence To Antiretroviral Therapy.

The guidelines for the treatment of HIV infected adults and adolescents (2005) calls for most people living with HIV many of whom are symptomatic to be treated with highly active antiretroviral therapy (HAART) for the rest of their lives.

Adherence to treatment is essential for successful treatment and has been reported to reduce virologic load, which is critical in reducing HIV related morbidity and mortality (Paterson *et al*., 2000; Ansten *et al*., 2000). Sub optimal adherence also leads to drug resistance, limiting the effectiveness of therapy (Walsch *et al*., 2000).

Recent studies have found an association between poor adherence and adverse virologic outcomes. Non-adherence in-patient on HAART was the strongest predictor of failure to achieve viral suppression below the level of detection (Shere, 1998).

Ickovics (1997) and Carmona (2000) both reported that 90-95% of the doses must be taken for optimal suppression, with lesser degree of adherence being associated with virologic failure. However, it is less certain what minimum thresholds are needed to maintain long-term suppression of HIV viral load (Chesney, 2000). Sub optimal adherence is common and survey has shown that one third of patient missed doses within less than three days of the survey. One fifth of HIV infected patient in one urban center never filled prescription forms. According to Leger and Leger Canadian survey, 82.9% of the 321 HIV patient surveyed admitted not following their treatment regimen to the latter. In fact, 45% revealed that they have missed at least one dose in the week preceding survey. For 35% of the participants, the number of pills represented an extremely important barrier to compliance. For 33% it was the dosing schedule and for another 33% the side effects of the drug were the problem (Williams and Friedland, 1997)

Other sources of instability influencing adherence include domestic violence and discrimination (Shapiro *et al*., 1999), medication side effects, and fear of experiencing morphologic side effect of the high active antiretroviral therapy (Max and Shere 2000). Selected factors such as race, low socioeconomic or educational level are not reliable predictor of sub-optimal adherence. Conversely higher socio-economic status and education level do not predict adherence to therapy (Luber *et al*., 2000).

In addition to the participation of family and friends, community interventions including adherence support groups or the addition of adherence to other support group agendas can help improve adherence. Optimal adherence requires full participation by health care team with goal re-enforcement by more than two team members. Improved adherence is associated with intervention that include pharmacist-based adherence to clinics and medication counseling and behavioral intervention (Mc phenson *et al*., 2000).

Measurement of adherence is imperfect and lacks gold standard. Patients self-report is a weakly predictive of the like hood of adherence, however an estimate of poor adherence by the patient has strong predictive value and should be regarded seriously (Stein *et al*., 1992).

Stenzel and his co-workers (2000) have enumerated various methods used to measure adherence which include

i. Directly observed therapy (DOT)
ii. Self report
iii. Provider assessment
iv. Pharmacy refill record
v. Pill counts
vi. Electronic monitoring
vii. Drug levels.

Regardless of the tool used to measure adherence, it is essential for the individual patient

to have a good understanding of HIV disease and the role medication plays in solving down the natural progression of the disease. The patient must have a fundamental belief in the medication and the primary care provider and health care team involved in his/her care. Before the first prescription is written the clinician must discuss and agree strictly with the patient on medications and consequence of non-adherence.

1.5.5 HIV Resistance to Antiretroviral Therapy

The usefulness of treatment of HIV infection is limited by the emergence of virus strains that resist antiretroviral therapy. This means that mutation in the virus genome allows HIV to reproduce even in the presence of therapeutic concentration of the drugs (Williams, 1998). Haubrich and colleagues (2001) observed reduced drug susceptibility to one or more protease inhibitors as the cause of treatment failure in 75% of the 69 patients failing a first protease inhibitors containing regimen. It was also demonstrated that, 6-12month after initiation of antiretroviral therapy in drug naïve patients that 70-90% can achieve maximal viral suppression yet in another setting only about 50% of patients achieved similar result (Deeks *et al*., 1999 and Lucas *et al*., 1999).

Viral resistance is the outcome of viral replication, mutation and selection. How quickly resistance occurs depends on the viral load (Durant *et al*., 1999). The result of several prospective studies indicate that the virologic response to a new antiretroviral regimen after virologic failure on a prior regimen can be significantly improved when result of resistance testing were available to guide choice of drugs in the new regimen (Dexter *et al*., 2000 and Torrel *et al*., 2002).

Inability to achieve maximal viral suppression generally occurs when there is sub therapeutic concentration of the drug in the body to inhibit viral replication. This most commonly occurs secondary to non-adherence of regimen. It may also occur secondary to drug interactions or pharmacogenetic variation causing enhance metabolism of the drug or simply because an inferior drug regimen was selected.

Various mechanisms of resistance are documented for various types of antiretroviral drugs and antiretroviral drug class. Two mechanism of nucleoside reverse transcriptase inhibitors drug resistance were shown to be through decrease incorporation (e.g stearic hindrance prevents productive binding of lamivudine to M184 V mutant reverse transcriptase enzyme) and increase removal of the drug like zidovudine (AZT) is exercised after it has been incorporated by AZT resistance reverse transcriptase enzyme.

Testing for HIV resistance to antiretroviral drug is a useful tool for guiding antiretroviral therapy (Hirsch *et al* 2003). Studies of treatment experienced patients have reported strong association between the presence of drug resistance identified by genotyping or phenotyping resistance assay and failure of the antiretroviral treatment regimen to suppress HIV replication (Cingolani *et al*., 2002; Durant *et al*., 1999 and Cohen *et al*., 2002.). Further more, when combined with a detailed drug history and efforts to maximize drug adherence, these assays have been shown to improve the short-term virologic response to antiretroviral therapy.

Resistance assays are useful clinically for patients experiencing virologic failure while on

antiretroviral therapy. Prospective data supporting drug resistance testing in clinical practice are derived from trials in which test utility was assessed for case of virological failure. These studies involved genotyping assay, phenotyping assay or both (Melnick *et al*., 2000; Tural *et al*., 2002).

Genotyping assay (sequencing). This looks at the presence of genetic mutation in HIV reverse transcriptase and protease gene sequences that may be associated with drug resistance. If the genetic mutation in person's virus match mutation assumed to confer resistance for a certain drug, then his or her virus is presumed to be resistant to that drug.
Phenotyping assay (susceptibility testing) directly measures the sensitivity of a patients HIV in response to a particular antiretroviral drug. The result of the test shows the amount of a particular drug needed to inhibit the growth of HIV by 50%. However, this test is lengthy and expensive to perform on a patient's virus sample and is not routinely employed in clinical management of a patient.
No prospective data exist to support using one type of resistance assay over another (genotyping versus phenotyping) in different clinical situations. Therefore one type of assay is recommended per sample; however for patients with complex treatment history, both assays might provide critical complementary information (Guidelines 2005).

1.5.6 Classes of Antiretroviral And Their Mechanism of Action

Currently there are four classes of antiretrovirals. These are:

1.5.6.1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Reverse transcriptase converts viral RNA into pro viral DNA before its

incorporation into the host cell chromosomes. The nucleoside reverse transcriptase inhibitors are nucleoside analogues that are potent inhibitors of HIV reverse transcription in HIV-1 and HIV-2. They specifically inhibit reverse transcriptase activity and cause termination of DNA polymerization after incorporation into the growing DNA strand of the virus (Kramer *et al*., 1986; Kohl *et al*., 1988).

All drugs in this class are substrates for reverse transcriptase. To become active, they first undergo phosphorylation by host cell enzymes in the cytoplasm. Phosphorylation is usually a three-stepped reaction into monophosphates to diphosphates and then to triphosphates. It is the triphosphates that are incorporated into and terminate DNA chain elongation. Example of members of this class are Lamivudine, Zidovudine, Stavudine, Didanosine, Zalcitabine and Emtricitabine

1.5.6.2. Non-nucleoside Reverse Transcriptase Inhibitors

They bind directly to reverse transcriptase and block the RNA-dependent and DNA – dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. They do not compete with template or nucleoside triphosphates hence do not require phosphorylation and are not active against HIV-2. These drugs were rationally designed to bind directly and non-compatibly to the active site of the reverse transcriptase following the discovery of the enzyme. Nevirapine does not inhibit HIV-2 reverse transcriptase and eukaryotic DNA polymerases (Van leth *et al*., 2004).

1.5.6.3 Protease Inhibitors

They act to inhibit both HIV-1 and HIV-2 replication through binding to the viral

protease enzyme. They effectively block the capability of this enzyme to process gag and gag-pol poly protein precursors into the key functional protein of HIV. These include the structural protein of the mature virion core and the viral enzyme of the newly produced viruses (proteases,reverse transcriptase, integrase and ribonucleosides) (Dragsteb *et al.,* 2003).

Classically, when Amprenavir binds to HIV protease, enzyme activity is inhibited and only inactive non-infectious virions are produced from the infected cells. Thus amprenavir stops the cycle of infection by ensuring that any newly assembled virions are unable to infect other CD4+.

1.5.6.4. **Entry Inhibitors**

There are three distinct crucial steps for entry of HIV into CD+4 T cells and thus corresponding anti retroviral agents are under pursuit (Christian *et al*., 2003). These agents are:

1. Attachment inhibitors: inhibit binding of HIV to the CD4+ receptors
2. Co-receptor antagonist: Inhibits binding to co-receptors.
3. Fusion inhibitors: They prevent HIV from entering target cells., which is involved in viral entry. Drugs of this class bind the HIV envelope protein gp41. by blocking the interaction between regions of the gp41 molecule, fusion inhibitors interfere with conformational changes (folding) of the envelope molecule required with the target membranes (eg enfurvitide).

Members of this class are not clinically being employed in the active management of HIV

infection but reserved to cases of resistance.

1.5.7 Clinical Anti-retroviral Combinations

Progress towards effective therapy of HIV infection began with observation that single agent zidovudine (AZT), didanosine (ddi) and zalcitabine (ddc) had activity against HIV infection in the laborator (Mitsuya *et al*. 1985, 1986.). Both zidovudine and didanosine have subsequently been shown to delay progression of HIV disease in patients (Fischl *et al*., 1987; 1990a; 1990b; Kahn *et al*., 1992)**.**

Combination therapy may provide greater clinical benefit in HIV disease through several mechanisms (Gail *et al*., 1999). First, a combination may exert a stronger antiretroviral effect than any single agent alone through additive or synergistic interactions. Second, combination therapies may reduce the short and long term toxicity associated with each drug, either by allowing the use of lower dose of each drug in combination or by utilizing cycles of each drug separated by rest period. Third, the use of combination therapy may delay the emergence of drug resistance thereby increasing the duration of drug efficacy or may broaden the spectrum against viruses already resistance to one component of the combination.

1.5.7.1 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI'S) Based Regimen (2NRTI's and 1 NNRTI)

This is the most widely studied combination and at present the most preferred (first line) treatment option (Anthony, 2003).

The panel on consensus report of practice guideline on the management of HIV patients (U.S.A) recommends.

i. Efavirenz+ (zidovudine or tenofovir or stavudine) + Lamivudine as preferred initial NNRTI's based regimen (except for pregnant women)
ii. Efavirenz + didanosine + Lamivudine (except for pregnant women) or Nevirapine based regimen (i.e. Nevirapine + Didanosine + Lamivudine).

The three NNRTI's (namely Delavirdine, Efavirenz and Nevirapine) are currently marketed for use. Delavirdine is the least effective and is generally not recommended for use as part of an initial regimen. Both Efavirenz based and Nevirapine based HAART were compared to triple NRTI's and protease inhibitors (PI Based) regimen as well as to each other.

Two studies compared the efficacy and tolerability of Nevirapine with Efavirenz. In one small study, after 48 weeks, 64% of 36 patients assigned to Nevirapine and 74% of 31 assigned to Efavirenz, each with stavudine and didanosine had a viral load less than 50 copies/ml. The 95% confidence interval for the difference was too wide to draw meaningful conclusion about similarity (or lack of there of) of efficacy (Nunenz *et al*., 2002).

The 2NN study was a much larger study that compared Nevirapine with efavirenz in antiretroviral naïve participants (Van leth *et al*., 2003). In the design of the 2NN study, a difference between the two treatment groups of 10% in treatment failure at 48 weeks was pre specified to be clinically meaningful (Van leeuwen *et al*., 2003). The result of the

study indicates that a difference of this magnitude cannot be ruled out. Furthermore, there appears to be more safety concern (particularly higher incidence and more serious skin rash and hepato-toxicity about using Nevirapine to Efavirenz.

The World Health Organization also in its guidelines on AIDS care recommends Zidovudine and Lamivudine taken twice a day and efavirenz at night as most promising combinations (Robbins *et al* 2003).

1.5.7.2 Protease Inhibitor Based Regimen (NNRTI's sparing).

Protease inhibitors in combination with Nucleoside reverse transcriptase inhibitors (NRTI's) have been evaluated in several controlled trials with clinical out comes (Hammer *et al*., 1997; Cameron *et al*., 1998; Florida *et al*., 2000 and Perez *et al*., 2002). This approach of combining protease inhibitor with NRTI's has rapidly become the preferential choice of initial treatment. When it is successful, one can expect response defined as a dropping of plasma HIV-RNA copy below 500 copies /ml in 70-90% of patients (Thomas *et al*., 1999). The dual nucleoside component should be chosen from zidovudine-lamivudine, stavudine-lamivudine, zidovudine-didanosine, stavudine-didanosine, and zidovudine-didanosine.

Initial studies established the superior efficacy of indinavir and ritonavir based regimens compared to nucleoside only regiment for AIDS or death among patient with advanced disease. Later head to head studies found that indinavir and nelfinavir were better tolerated than ritonavir (Katzenstein *et al*., 2000).

The study of nelfinavir versus ritonavir established that nelfinavir was better tolerated than ritonavir and had clinical immunologic and virologic efficacy that was nearly as great as ritonavir.

In a study carried out by Cisse et al (2005) to study the twelve month result of a boosted protease inhibitors strategy with ritonavir 100mg/indanavir 400mg in HIV-1 infected patients in Mali, it was found that despie the local conditions of heat and difficulties to store ritonavir), the use of indinavir/ritonavir twice a day was feasible and potent (in comparison to the conventional thrice dosage regimen)

1.5.7.3. Triple NRTI's Regimen (Both NNRTS AND PI" Sparing)

Another approach to antiretroviral therapy is to use triple NRTI's combination. Potential advantage of the 3NRTI's strategy are to spare protease inhibitors and NNRTI's for later used, to avoid PI or NNRTI's associated adverse effects (Kumar *et al*., 2002) and minimal drug-drug interactions. Some clinicians however, have concern over the potency of this single class regimen as well as potential of development of more NRTI's mutation and limitation of future treatment options.

In a study carried out by schlomo *et al*., (2003), abacavir- lamivudine- zidovudine in antiretroviral naïve HIV infected adults was Equivalent to the regimen of indinavir-lamivudine–zidovudine in achieving plasma HIV RNA level of less than 400 capies/ml at 48 weeks . In the atlantic study, the virologic and imunologic efficacy of stavudine (d4T) plus didanosine (ddi) in combination with either nelfinavir, nevirapine or Zidovudine in an antiretroviral naïve subjects shows that virologic response of both PI and NNRTI

based regimen were found to be superior to the stavudine/didanosine/zidovudine combination at 96 weeks (Van leeuwen *et al*., 2003).

In a randomized study evaluating the efficacy and tolerability of continued treatment with protease inhibitor plus nucleoside analogue combination regimen and a simplified regimen of abacavir-Lamivudine–zidovudine (3NRTI's) in patient with suppressed human immuno deficiency virus type-1(HIV-1) RNA for more than 6month who did not have the transcriptase 215 mutation. After a median follow-up of 84 weeks, virologic failure was 6% in the continuation and 15% in the simplified group. Study treatment was discontinued because of adverse events in 20% of the continuation and 7% of the simplified group. Thus simplification to abacavir-Lamivdine –Zidovudine significantly decreases non fasting cholesterol and triglyceride level however carries a risk of virologic failure when treatment history or resistance testing suggest the presence of archived resistance mutation in the simplified regimen (Milos *et al*., 2002).

1.5.8 **Toxicity/Adverse Clinical Event to HAART**

A number of class-related toxicities have been recognized and attributed to antiretroviral agents since their approval. Some of these toxicities are potentially serious and may limit patient's ability or willingness to remain on therapy (John and Joel 2003). The following are some of these documented toxicities/side effects.

1.5.8.1 Lipodystrophy:

Lipodystrophy is reported in 20% - 80% of patients receiving antiretroviral therapy, a wide range reflecting heterogeneous population and the lack of standard case definition

(Hadigan *et al*., 2001; Moore et *al*., 2005).

Fat accumulation (lipodystrophy) has been more closely linked to use of protease inhibitors, but it is now clear that nucleoside analogues play a role in the development of lipotrophy. The most significant association is with stavudine or stavudine/didanosine, although AZT may also cause fat loss (Dube *et al*., 2000).

1.5.8.2 **Lactic Acidosis/Hepatic Steatosis And Hepatotoxcity**.

Hyperlactatemia can be asymptomatic or can be associated with overt, sometimes fatal lactic acidosis. It appears to be a complication of NRTI therapy and although it was originally described as a rare but potentially fatal complication of AZT therapy in the early 1990s, it is now seen primarily as a complication of d4T therapy (Lucas *et al*., 1999). NRTIs induced lactic acidosis may appear with hepatic steatosis among the NRTIS. stavudine may add to the risk of hepatotoxicity among people taking ritonavir/saquinavir (Giseof *et al*., 2000).

All antiretroviral agents have been implicated as potential causes of hepatotoxity. Protease inhibitors especially ritonavir can cause hepatoxicity and hepatitis also occurs with NNRTIs especially Nevirapine (Bersoff *et al*., 2001; Coglan *et al*., 2001).

1.5.8.3 Ostepenia, Osteoporosis and Osteonecrosis.

Osteonecrosis and avascular necrosis is another possible late complication that may be due to HAART. There have been 67 reported cases of osteonecrosis in HIV infected

patient (Carr, 2001).

Reported prevalence based on routine magnetic resonance imaging (MRI) scan is 1.3% to 4.4%. A survey of 23 cases of symptomatic avascular necrosis in two Spanish provinces found a marked jump in diagnosis since protease inhibitors became widely used but seven of the people with avascular necrosis never took protease inhibitors (Gutierrez *et al*., 2002).

1.5.8.4 **Pheripheral Neuropathy**

Several drugs taken by people with HIV infection can cause peripheral neuropathy; a condition characterized by tingling numbness or burning that start in the feet and spread to the hands. The most common drug classes are the nucleoside didanosine (ddi), stavudine (d4T) and Zalcitabine (ddc). A study of 1,117 people taking ddi and or d4T and or hydroxyurea found that most neuropathy occurred with ddi/d4T/hydroxyurea followed by ddi/d4T, ddi/hydroxyurea, d4T alone and Zalcitabine (Moore *et al*., 2000).

1.5.8.5 **High Blood Glucose And Insulin Resistance**.

Several studies implicate PI's in insulin resistance even in people without lipodystrophy or without HIV infection (Carr *et al*.,1998, Hadigan *et al*., 2001). Insulin resistance presides and contributes to visceral adiposity in people taking protease inhibitors. Amprenavir and atazanavir may be an exception.

1.5.8.6 **Diarrhoea and Nausea.**

FDA approval for product information for nearly every antiretroviral lists diarrhea, nausea or both as side effects. Although these gastrointestinal problems can be hard to escape with any regimen, protease inhibitors are probably the leading causes. Gastrointestinal toxicity and pheripheral neuropathy were the main reasons for switching from an effective first line PI regimen in one study of 775 people (Deleman *et al*., 1998).

1.5.8.7 Hypersensitivity Reaction

Although trimethoprin/sulfamethaxazole is the drug most frequently implicated in such reactions in HIV patients, five of the currently available antiretrovirals have been described to induce hypersensitivity reactions or syndrome. These include abacavir, amprenavir and all the non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine and efavirenz). These reactions are for the most times idiosyncratic and unanticipated (Piliero *et al*., 2001).

1.6 JUSTIFICATION FOR THE STUDY

With the rapid evolution of new highly active antiretroviral therapy (HAART) drugs regimen, there is the fear that many would not be prescribed or used properly. This poses a great danger of an early development of resistance to painstakingly developed treatment regimen, which could set us decades back in the global fight against the HIV/AIDS pandemic.

Equally important in the justification of the study is the cost affordability and the level of compliance to these newly developed drugs regimen especially in our community, which is characterized by widespread poverty, high illiteracy level and poorly developed

healthcare delivery system.

Having appreciated the consequences of an inadequate attention to proper care/management of HIV/AIDS, the Federal ministry of health prescribed a guideline on the use of antiretrovirals (especially with regards to the principles of drug treatment) and made available very subsidized antiretrovirals. This study will also provide some useful information that will improve the future planning of ARV treatment programmes in Nigeria.

1.6 STUDY OBJECTIVES

a. General objective

i. The general objective of the study is to asses the rational use of antiretroviral drugs used in three different health institutions within Kano metropolis.

b. Specific objectives

i. To determine the different types of antiretroviral treatment programme employed in Kano for management of HIV/AIDS.

ii. To compare the different antiretroviral programme in Kano with the prescribed National Guidelines on antiretroviral therapy.

iii. To determine the accessibility and affordability to antiretroviral therapy in Kano.

iv. To determine the level of compliance/adherence to antiretroviral therapy by individual patients in Kano.

CHAPTER TWO

MATERIALS AND METHODS

2.1. STUDY LOCATION - KANO

Kano, which is the capital city of Kano State, is located at latitude 12.0^0N and longitude 8.15^0E. It is the largest and most populous urban town in Northern Nigeria and is ranked second to Lagos nationally. It has an approximate population of 3.33 million inhabitants with a population density in excess of 250 peoples per square mile (Mathew, 1993).

Demography follows a classical cosmopolitan area. Majority of the people are muslims (more than 90%) and practice polygamy. Kano as a cosmopolitan town is made up of six local governments namely:

1. Municipal Local Government
2. Nassarawa Local Government
3. Fagge Local Government
4. Dala Local Government
5. Tarauni Local Government
6. Gwale Local Government

The town has also overlapped into many communities within the neighboring local governments of Kumbotso, Ungogo and Gezawa Local Governments. The healthcare delivery system consists of two tertiary/teaching Hospitals, two specialist hospitals and seven general hospitals in addition to more than seventy private clinics.

Kano being a highly commercial town, receives visitors and immigrants from other neighboring and far states and even from neighboring countries of Niger, Chad and Cameroon thereby making it rapidly growing and expanding in size.

2.2 STUDY SITES

2.2.1 **Aminu Kano Teaching Hospital Kano**

The present Aminu Kano Teaching Hospital historically proposed at the council of health meeting No. 15 of 1974 came into operation in March 1994 temporarily at Murtala Mohd specialist Hospital. The hospital moved to its present location (permanent site) in July 1997. According to planning, statistic and record department (2004) of the hospital, the 2001 and 2002-year patient annual enrolment stood at:

	Year reviewed	**2001**	**2002**
-	General out patient attendance	54,232	52,126
-	Consultants clinics	42,187	56,568
-	Accident and emergency	10,753	14,403
-	Total	107,174	123,102

Currently, the hospital is one of the centers enlisted for a national programme on HIV/AIDS having approximately 2000 patients on subsidized antiretroviral therapy.

2.2.2 **Mohammad Abdullahi Wase Specialist Hospital**

Formerly known as Nassarawa hospital, the hospital was opened on 7th march 1934 and it is situated at the Nassarawa G R A. part of the Kano town. The hospital used to offer a

limited range of medical care until it was upgraded to a specialist Hospital that offer full medical services in the major specialties of medical care. Currently the hospital has a total patient bed capacity of 210 and is being headed by a medical director and holds a status of a zonal center of the health services management Board. The average annual patient enrollments stand at about 120,000.

2.2.3 **Premier Clinic**

This is a specialist private hospital offering consultant care in medicine, pediatrics, Obstetric & Gynaecology and urology. The hospital is fully owned and managed by a consortium of indigenous specialist medical practitioners. Because of socio-cultural as well as premium services offered, the hospital maintains excellent patronage from the upper and middle class patients as well as those on retainer ship from their institutions.

The hospital was established in January 1995 at Aminu Kano Way before moving to its present address at No. 8 1st Avenue Hausawa in January 1997. The hospital now has an average daily patient turn out of about 40.

2.3 **STUDY DESIGN**

The study was conducted as a descriptive cross sectional one.

2.4 **STUDY POPULATION**

The study populations were adults' confirmed HIV/AIDS patients receiving antiretroviral treatment in the three-selected health institution. The number of patients in each hospital is drawn on a proportionate number of patients in each hospital to the total number of

patients put together.

2.5 SAMPLE SIZE DETERMINATION

The sample size was determined based on the following formula:

$$\text{Sample size (n)} = \frac{Z^2PQ}{d^2}$$

Z = value of constant at 95% confidence interval

P = Rural prevalence of HIV/AIDs in Kano

Q = Complementary probability = (1-p)

d = Level of error allowed

For this study,

P = 9.3% (Based sentinel survey of 2001 on the prevalence of HIV in rural areas of Kano State)

Z = 1.96

Q = (1-p) = 0.927

d = 5% = 0.05

$$\text{Thus: } n = \frac{1.96 \text{ x } 1.96 \text{ x } 0.093 \text{ x } 0.927}{0.05 \text{ x } 0.05} = 132$$

In order to increase precision and to reduce attrition rate, 138 accessible subjects were recruited for the study.

2.6 SAMPLING TECHNIQUES

The sampling technique for this study is based on stratified sampling by proportionate

allocation to determine the number of patients in each institution and then by simple random sampling within each study site (Hospital). Thus the sampling technique is a multistage sampling technique.

2.7 PREPARATION FOR DATA COLLECTION

An official letter from the department of Pharmacology, Ahmadu Bello University Zaria was collected requesting for an approval of the study at the respective hospitals. The letter was channeled through the hospital ethics committee which later gave an approval for the study. An informed consent was obtained from the participating subjects.

2.8 DATA COLLECTION TECHNIQUE

For the actual data collection, the following were used.

1. A standardized, pre-tested, structured questionnaire that is mostly close ended in nature and researcher administered.

Direct answers by the patient were not possible because of the anticipated high level of illiteracy.

2. Patient's medications information obtained from his/her case folder.

2.9 DATA ANALYSIS

The data obtained was entered into a spreadsheet and then analyzed using the computer software called statistical programme for social science (SPSS). The result is presented in the form of simple tables using Microsoft word . Appropriate statistical test of significance using simple percentage was used to determine association between

categorical variables.

2.10 LIMITATIONS OF THE STUDY

1. The study was only restricted to adults patients as pediatrics were not included.
2. Also the study was limited to a short term period of only about four months
3. Lack of adequate patient's record and other laboratory evaluations limited the degree of data correlations and interpretations

CHAPTER THREE

RESULTS

This case study was carried out covering a period of about four month between October 2003- January 2004. The following table represents the major results of the study.

Table 3.1 Distribution of subjects Among the Health Institutions.

S/NO.	LOCATIONS	FREQUENCY	PERCENTAGE %
1	AKTH	100	72.5
2	MAWSH	27	19.5
3	PREMIER CLINIC	11	8.0
	TOTAL	138	100%

From Table 3.1 above, the total number of patients that participated in the study were 138. Out of this total, 100 patients representing 72.5% were from Aminu Kano Teaching Hospital, 27 representing 19.5% and 11 representing 8.0% were from Mohammed Abdullahi Wase Specialist Hospital and premier clinic respectively. This level of distribution do not equate with the whole number of HIV/AIDS patients attending those institutions rather represent a proportionate number of HIV/AIDS receiving treatments that are assessable and willing to participate.

Table 3.2 Sex Distribution

S/NO	LOCATION	SEX		TOTAL
		MALE	FEMALE	
I	AKTH	52 (52%)	48 (48%)	100 (100%)
2	MAWSH	19 (70%)	8 (30%)	27 (100%)
3	PREMIERE	8 (73%)	3 (27%)	11 (100%)
	TOTAL	79 (57%)	59 (43%)	138 (100%)

Analysing Table 3.2 above on the gender distribution among the subject showed that 79 patients representing 57% were males while 59 patients representing 43% were females. The result also analyzed within individual hospital reveals similar pattern with high number of males over females. However the result should not erroneously be used to conclude that more males are infected with HIV/AIDS than females but to only indicate more males are seeking treatment than females.

3.3 Age Distribution

From the analysis of the result, the mean age distribution of the subject was 35.6 years with a minimum age of 22 years and maximum age of 55 years while the modal age range is 31-40 years. Also from the study the minimum age of the subject for both males and females was 22 years. The mean age of the female subjects was 31.1 years with a standard deviation of 16.4 while that of males was 39 years with a standard deviation of 7.0.

Table 3.4 Occupational Distribution.

S/NO	OCCUPATION	FREQUENCY	PERCENTAGE
1	CIVIL SERVANT	45	33%
2	BUSINESS MEN/WOMEN	46	33%
3	UNEMPLOYED/ STUDENTS	6	4%
4	HOUSE WIVES AND OTHERS	41	30%

Table 3.4 above revealed occupational distribution of the subjects with 45 of them representing 33% as civil servants while 46 of them representing about 33% were business men/women. Unemployed and students represent the smallest percentage of the occupation distribution chart with only about 4%. Housewives and others including windows and truck drives represent another good segment of the occupational chart table representing about 30%.

Table 3.5 Educational Levels of The Patients.

S/NO	EDUCATIONAL LEVEL	FREQUENCY	PERCENTAGE

1	NONE	4	3%
2	QUR'ANIC	8	6%
3	PRIMARY	20	14.5%
4	SECONDARY	49	14.5%
5	TARTIARY	57	41%

Table 3.5 above representing educational level showed that the higher the educational level of the patients, the higher their frequency in seeking medical treatment. However, the result should not be used conversely to predict that the higher the educational level of the subjects, the higher the incidence of HIV/AIDS infection since this is a stratified or class study.

Table 3.6 Ethnic Variables among Patients.

S/NO	TRIBE	FREQUENCY	PERCENTAGE
1	HAUSA/FULANI	80	58%
2	YORUBA	6	4%
3	IGBOS	29	21%
4	OTHERS	23	17%

The ethnic distribution table above showed that the Hausa/Fulani constitute about 58% of the total subject receiving treatment studied. The Yorubas were 4%, Ibos were 21% while others constitute 17%. Analyzing this result, inference can be made that the higher

number of Hausa/Fulani could most likely be a location or study factor. The Ibos are well travelled and highly enterprising and this could explain their somewhat higher percentage. Among the groups of others the kajes, Ibiras, Ijaws, Idoma and Igalas are the most predominant and certainly indigenous to the areas recorded to have the highest incidence of HIV/AIDS based on the sentinel survey of 2001 and 2003.

3.7 Religion

S/NO	RELIGION	FREQUENCY	PERCENTAGE
1	MUSLIMS	90	65%
2	CHRISTIANS	48	35%

Religious distribution among the patients as from table above showed that Muslims seeking treatment among the group studied represent 65% while the Christians represent 35%. However this result can only be viewed as a location factor.

3.8 Marital Status

S/NO	MARITAL STATUS	FREQUENCY	PERCENTAGE
1	SINGLE	23	17%

2	MARRIED	97	70%
3	DIVORCED	4	3%
4	WIDOW	14	10%

Marital status among the subjects showed that 17% were single, 70% were married, 3% were divorced and 10% were widowed. Most of the widows have their partners died either as a result of a confirmed HIV infection or HIV related clinical conditions.

Cross tabulating marital status with the location of treatment showed that all the divorced and most of the widowed patients attended Aminu kano Teaching Hospital only where federal government subsidized form of treatment is available.

3.9 Partners Distribution among subjects.

Among the married subject across both genders, the percentage of those living with one partner was 75% while those living with multiple partners (either a husband living with more than a wife or a wife married to a husband with more than a wife) were 25.0%. Thus 25% have multiple sex partners.

3.10 Treatment Affordability.

Among the subjects receiving treatment, 98% of them can continue to afford the treatment based on the subsidize hospital supply at One thousand (N1,000) naira per month while about 2% claimed non-continuous affordability (as evidence by a skipped

doses). However using a monthly supply at an estimate chemist price of about Ten thousand naira (N10, 000), only 47.5% claimed continuous affordability despite the grave consequences of the disease. Further analysis of the percentage of those claiming non-continuous affordability showed that most of them receive their treatment from Aminu Kano Teaching Hospital.

Table 3.11 Treatment Duration.

S/NO	PERIOD RANGE (MONTH)	FREQUENCY	PERCENTAGE
1	1-5	23	16.7
2	6-10	30	21.7
3	11-15	54	39.1
4	16-20	26	18.9
5	21-25	2	1.4
6	26-30	1	0.7
7	31-35	1	0.7
8	36-40	1	0.7

Patients' duration on antiretroviral regimen varies from one month to 37 month with the mean duration of treatment as being 11.34 month and a standard deviation of 5.8 month. The modal period of treatment is 11-15 months.

Table 3.12 Antiretroviral Combinations Employed/ Used.

S/NO	TYPE OF ARV.	FREQUENCY	PERCENTAGE
1	LAMIVUDINE/ZIDOVUDINE	16	12
2	LAMIVUDINE/STAVUDINE/NEVIRAPINE	97	70
3	LAMIVUDINE/ZIDOVUDINE/NEVIRAPINE	25	18

The result of the study from Table 3.12 above showed that 12% of the subjects were on Lamivudine/ zidovudine (dual nucleoside regimen) antiretroviral regimen while 70% were on the subsidized (Lamivudine/stavudine/nevirapine) highly active antiretroviral regimen (HAART) and 18% being on lamivudine, zidovudine and nevirapine antiretroviral regimen.

In terms of the individual health institutions, of the subjects receiving treatment at Aminu Kano Teaching Hospital, 97% of them were on Lamivudine/stavudine/nevirapine. This highly unified treatment pattern was because of the availability of the subsidized treatment regimen while the remaining 3% were on lamivudine, zidovudine and nevirapine (with the nevirapine obtained from the subsidized stock.)

In Mohammed Abdullahi Wase Specialist Hospital, 60% of the subjects were on the dual nucleoside therapy of lamivudine and zidovudine (combivir) only while the remaining 40% were on triple combination of zidovudine/lamivudine/nevirapine

At premier clinic, all the patients (100%) were on triple therapy of lamivudine/zidovudine/nevirapine.

Table 3.13 Sources of Antiretrovirals

S/NO	Sourcing Point	FREQUENCY	PERCENTAGE
1	Hospital	96	69%
2	Chemist	30	22%
3	Manufacturers	12	9%

Table 3.13 above revealed that because of the presence of the subsidized therapy at the hospital, almost 70% of the patients receive their treatment from the hospital while 22% and 9% from retail pharmacy outlet and manufacturers respectively. Also, the patients sourcing their antiretrovirals from the hospital are from AKTH.

Table 3.14 Distribution of Missed doses among subjects

S/NO	MISSING STATUS	FREQUENCY	PERCENTAGE
1	YES	81	58.7%
2	NO	57	41.3%
	TOTAL	138	100%

Table 3.14 above indicates that of the total 138 subjects that participated in the study,

about 60% of them admitted ever missing a dose of their treatment whilst 40% of them claimed complete adherence to treatment. This alarming high figure of non-adherence could explain some of the reasons for treatment failure/ resistance already established in some patients. The study also revealed that at least 25% of the patients missed a dose within a week preceding the study. This result closely equate with result obtained in other study. The mean dose missed from the study is 3.71 with a standard deviation of 5.4. The least dose is a single dose and the highest dose is 28 doses (2 weeks treatment course). Detailed analysis of the incidence of missed medication showed a higher incidence in premiere clinic followed by MAWSH over AKTH.

Inquiry into association between the degrees of the disease symptoms with the incidence of missed doses indicated a higher incidence in those on longer treatment duration where there is mark reduction in symptoms score.

TABLE 3.15 Distributions of Factors Responsible For Missed Doses

S/NO.	Factors responsible	Frequency	Percentage
1.	Side effects	9	11.6%
2.	Fasting	16	20.7
3.	Forgetfulness	14	18.2
4.	Fear of discrimination	8	10.3
5.	Treatment cumbersome	15	19.4

6.	Traveling	7	9.0
7	Unavailability	8	10.3
	Total	77	100 %

From Table 3.15 above, it revealed many factors to be responsible for missed doses observed among the patients taking antiretrovirals. Side effects particularly skin rashes accounted for about 12% of the patients that reported missing their medications. Fasting was reported to be responsible for the highest case of missed dose among the patients with about 21%. However this could have been because the study was carried out during the fasting period of Ramadan. About 18% of the patients missed their medication because of forgetfulness, as the treatment schedule is indefinite. Also a whooping 19.4% of the patients missed their medication because of the cumbersome nature of treatment claiming that treatment is non curative. An insight analysis into this group of patients revealed them to belong to those on longer duration of treatment and in those with improved clinical response. Other factors responsible for missed doses were fear of stigmatization, traveling and unavailability represented by 10%, 9% and 10% respectively.

TABLE 3.16 Distributions of Patients That Have Stopped Treatment.

S/NO	TX. STOPPED STATUS	FREQUENCY	PERCENTAGE
1	YES	19	13.9%

2	NO	118	86.1%
	TOTAL	137	100%

From table above, it showed that as much as 86% of the total subjects receiving the antiretroviral regimens have been on same treatment without being stopped secondary to any cause. However, about 14% of them were advised to stop treatment principally because of either of active tuberculosis, pregnancy and or adverse drug reaction (severe skin rashes in form of exfoliative dermatitis).

TABLE 3.17 Distributions of Positive Partners Among Patients.

S/NO	PARTNER STATUS	FREQUENCY	PERCENTAGE
1	POSITIVE (+VE)	67	57.8
2	NEGATIVE (-VE)	28	24.1
3	NOT DETERMINED (ND)	21	18.1
	TOTAL	116	106.0

From the distribution table above, it can be seen that among the patients receiving

treatment who have partners (and recent widows) 58% of them have their partners tested positive while 24% and 18% of them are negative and undetermined respectively.

TABLE 3.18 Distributions of Positive Partners Receiving Treatment

S/NO	PARTNER TREATMENT STATUS	FREQUENCY	PERCENTAGE
1	YES	42	70%
2	NO	18	30%
	TOTAL	60	100%

Among the positive partners, the percentage of those receiving antiretroviral regimen is 70% while 30% of them are not receiving treatment. Being not on treatment could vary with many factors including financial inability or the partners CD4+ has not fallen to a level of initiating treatment.

CHAPTER FOUR

DISCUSSION, CONCLUSIONS AND SUGGESTIONS

The prevalence of HIV/AIDS continue to rise with the result of the 2003 sentinel survey being 5.0% (marginally different for 2001 survey having 5.8%) and also coupled with the increasing number of patients trooping to the clinic everyday seeking treatment either of the clinical syndrome of the disease condition or of the opportunistic infections associated with the disease.

The result of this study carried out to determine among other things, the various antiretroviral treatment programme in some selected health institutions within Kano metropolis, showed that more men are seeking treatment in comparison to women (57% versus 43%). It is equally revealing from the study that the mean age of the population is 35.6 years with a standard deviation of 7.8 years. The modal age range is 31-40years which constitute 41% of the total population.

Other socio political as well as demographic data revealed that the ravage of HIV/AIDS infection affect all crannies of the society with the result obtained in this study not strikingly different from others except for the influence of the location factor which gives higher percentage to the Hausa/Fulani among other tribes and to Muslims over Christian among the patients receiving antiretroviral regime.

The Nigerian Standard Treatment Guideline was developed with a strategy to simplify regimen by reducing the number of pills and frequency of dosing as well as minimizing

drug interaction and side effect. Recommended combinations entail the use of two-nucleoside reverse transcriptase inhibitors (proven and safe combination) together with a third regimen derived from the following combination.

1 Indinavir + ritonavir - - protease inhibitors (PI) based

2 Ritonavir + lopinavir - - "

3 Efavirenz or nevirapine - - NNRTI's based.

The guideline highlighted that many experts recommended a protease inhibitors plus two nucleoside reverse transcriptase inhibitors (2NRTI'S) as preferred starting regimen. However, though no comparative efficacy trials have been carried out, the demonstrable ability of efavirenz in combination with 2NRTI'S to suppress viral replication and increased CD4+ to a similar degree as protease inhibitors plus 2NRTI'S support a preference for efavirenz over available NNRTI'S. The guidelines also re-emphasize the contra-indicated use of monotherapy except in pregnancy to prevent mother to child transmission.

The result of this study showed that there was 88.4% compliance for the recommended triple highly antiretroviral treatment (HAART) programme and 11.6% non-compliance. Aminu Kano Teaching Hospital antiretroviral programme was in full compliance with the recommended guideline of triple antiretroviral drugs combination courtesy of the federal government subsidized treatment option taking 97% (Lamivudine, Stavudine and Nevirapine) while other treatment plans take 3% (Lamivudine, Stavudine and Nevirapine). All patients receiving their antiretroviral regimen from premiere clinic were

also on triple combination of Lamivudine, Stavudine and Nevirapine. At Mohammed Abdullahi Wase Specialist Hospital (MAWSH) the compliance level was only 40% as this represent the percentage of the patient on triple antiretroviral combinations (Zidovudine, Lamivudine and Nevirapine) whilst the remaining 60% were on dual therapy of nucleoside reverse transcriptase inhibitors (2NRTI'S) of Lamivudine and Zidovudine only. In this institution, the prescription pattern was not the treatment guideline of the hospital rather the discrete decision of the prescribing practitioner.

Compliance has always being a serious subject of concern especially to a chronic disease condition requiring a continuous or an indefinite treatment plan such as HIV/AIDS. The success and or otherwise of the result of adherence to treatment dictates the prognosis of HIV/AIDS management. Where it has been studied, non-adherence to treatment with antiretroviral regimen has been as high as 70% (Anjorin 2005). The result of this local study showed a similar pattern of high level of non adherence to treatment with 60% of the subject studied recording non-complete adherence because of missed doses. It is equally revealing that at least 25% of the subject studied admitted missing a dose of their medication within a week preceding the study. Various reasons were attributed to non-adherence and which include fasting, highly cumbersome (continuous) nature of the treatment plan, forgetfulness, side effect (Skin –rash), fear of stigmatization and non-availability.

In the third world economy typified by ours (Nigeria) the principal success or otherwise of any treatment plan is much dependent on the affordability and availability of such

treatment options and where the issue becomes more paramount is when it is associated with disease condition that affects mostly the lower socio-economic strata of the society. The result of this study relative to the affordability and availability of various antiretroviral programme showed that the subsidized federal government treatment plan is highly affordable with 98% of the patients (and all those from AKTH) admitting affordability at the rate of one thousand naira per month supply (N1,000).

However the response pattern changed if the patients were to source it from a retail pharmacy out let or from a manufacturer's representative where the monthly supply can cost up to ten thousand naira (N10, 000).

The percentage of those claiming affordability of a month supply at ten thousand naira, is only 47.5% compared to 52.5% of them claiming non-affordance even after weighing the deadly consequence of non-treatment.

It is highly consequential for us to appreciate that, those patients/ subjects studied represent only a small fraction of the high proportion of the patient load of people living with HIV/AIDS. If the study is to include the higher proportion of non opportune patients, the result will certainly indicate a grave danger ahead unless a special and all encompassing treatment plan is provided at a special discounted price since

CONCLUSIONS

Based on the findings of the research carried out, the following conclusions can be

derived:

1 HIV/AIDS is pandemic affecting both males and females across both religious groups in Nigeria. It leaves no boundary in the socio-economic strata.

2 Aminu Kano Teaching Hospital and Premiere Clinic were fully compliant to the Standard Treatment Guidelines of HIV/AIDS patient which recommends the use of highly active antiretroviral drugs (HAART) in a triple combinations while Mohd. Abdullahi Wase Specialist Hospital (MAWSH) was 40% compliant with about 60% on dual nucleoside reverse transcriptase inhibitors therapy. However it is to be noticed that this practice was only at the discretion of the prescribing practitioner.

3 Mohammad Abdullahi Wase specialist hospital was not HAART compliant.

4 Adherence to antiretroviral regimen was difficult with about 60% of the patients from the study having ever missed a dose in the treatment schedule. 25% of the patients have missed at least a dose within a week preceding the study. The average number of dose missed is 3.71 with a standard deviation of 5.4. The minimum dose missed was a dose and the highest been 28 doses (2 weeks doses).

5 Factors responsible for missed doses were as a result of fasting, cumbersome treatment schedule, forgetfulness, side effects(mainly rashes), stigmatization and unavailability (because they have not filled prescription)

6 Antiretroviral drugs were available either from a hospital source, a retail pharmacy outlet or directly from manufacturer's representative. Their affordability was what remained quarry some. About 97% of the patients maintained their readiness to continue affording the drug at the subsidized federal government supply price of one thousand naira (N1000.00) per month whereas only 47.5% of them accepted the

possibility of affording the retail price of ten thousand naira only (N10,000.00) per month despite the grave consequences of the disease.

7 Antiretroviral drugs used in the management of HIV/AIDS in kano are mostly drawn from the following:

i. Lamivudine.

ii. Zidovudine.

iii. Stavudine.

iv. Nevirapine

SUGGESTIONS.

Although the principal objectives of this study was to determine the level of compliance to the standard treatment guideline by the selected (studied) health institutions, availability and affordability of the various antiretroviral regimen as well as determining the level of adherence to prescribed antiretroviral regimen among the studied population, it still explored opportunity for improvement and confronting the scourge of HIV/AIDS in our local community. The following recommendations are hereby suggested.

1 There is a need for an improved and proper record keeping towards each patient as an individual in all the health institution studied.

2 The Federal Government should broaden the subsidized antiretroviral regimen to accommodate more patients as the number of patients dying in the queue of joining the scheme is high because of higher cost of other treatment.

3 The CD4+ and plasma RNA should be monitored more closely at least every three month. This is especially more important for patients receiving treatment outside

AKTH.

4 Federal Government should make available the facility for resistance testing to provide more appropriate the methodology of the choice of salvage therapy.

5 Salvage therapy that will include other new antiretroviral should also be made available to take care of resistance already established with the conventional Lamivudine/Stavudine/Nevirapine Combination.

6 There is need for increasing campaigns against stigmatizing HIV/AIDS patients such that they can feel free to take medication in other presence.

7 Patients need to be well informed about their medication and the danger posed by skipping a dose. In fact, they should be properly informed on how to take the medication during fasting period.

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APPENDIX 1

NNRTI Based Regimen (1NNRT1 + 2NRTI'S)

Panel Recommendation

Preferred NNRTI- based regimen

1 Efavirenz + (zidovudine or tenofovir) + (lamivudine or Emtricitabine) except during first trimester of pregnancy.

Alternative NNRIT based regimen

2 Efavirenz + (didanosine or abacavir or stavudine) + (lamivudine or emtricitabine) except during pregnancy particularly during first trimester.

3 Nevirapine based can be used as an alternative.

The panel does not recommend the following as initial therapy

delavirdine- due to its inferior antiretroviral potency and three times dosing.

PI-Based Regimen (1 or 2 PI'S + 2 NRTIS)

Preferred P.I. based regimens

1 Lopinavir/ ritonavir +zidovudine + (lamivudine or emtricitabine)

Alternative P1 based regimen may include.

2 Atazanavir, fosamprenavir, ritonavir-boosted fosamprenavir, ritonavir-boosted indinavir, nelfinavir or ritonavir-boosted saquinavir or abacavir or didanosine) + (lamivudine or emtricitabine)

3 Lopinavir/ritonavir + (abacavir or stavudine or tenofovir or didanisine) + (lamivudine or emtricitabine).

Triple Nucleoside Reverse Transcriptase Inhibitors Regimen

Panel's Recommendation

1 A 3-NRTI regimen consisting of abacavir,zidovudine and lamivudine should only be used when a preferred or alternative NNRTI—based or PI-based regimen can not or should not be used as first line therapy.

2 The panel does not recommend the use of the following 3NRTI's based regimen as sole ARV combinations

Abacavir+tenofovir+lamivudine

Didanosine+tenofovir +lamivudine

Selection of dual nucleoside based back bone as part of initial combination therapy should be:

1. zidovudine or tenofovir + lamivudine or emtricitabine as the 2NRTI's back bone
2. stavudine or didanosine or abacavir +lamivudine or emtricitabine may be used.

ANTIRETROVIRAL THAT SHOULD NOT BE OFFERED AT ANYTIME

A. REGIMEN NOT RECOMMENDED.

1 Monotheraphy

2 Dual nucleoside regimen

3 3 NRTIS regimen of abacavir + tenofovir + lamivudine (or emtricitabine).

4 3 NRTIS regimen of didanosine + tenofovir +lamivudine (or emtrcitabine).

B. ANTIRETROVIRAL COMPONENT NOT RECOMMENDED

1 amprenavir oral solution

2 amprenavir + fosamprenavir

3 amprenavir oral solution + ritonavir oral solution

4 atazanavir +indinavir

5 didanosine + stavudine

6 didanosine + zalcitabine or stavudine + zalcitabine

7 emtricitabine + lamivudine

8 lamivudine + zidovudine

9 stavudine + zalcitabine.

DOSAGES OF ARVS FOR ADULTS

DRUGS	**DOSE**
NRTI's	
Zidovudine (zdv)	30mg twice daily
Stavudine (d4t)	40 mg twice daily
Lamivudine (3TC)	150mg twice daily
Didanosie (ddi)	400mg twice daily
Abacavir (ABC)	300mg twice daily
Emtricibine	
NNRTI's	
Efavirenz (EFZ)	600mg once daily
Nevirapine (NVP)	200mg once x2/4 then 200mg BD
Delavirdine	
PROTEASE INHIBITORS	
Nelfinavir (NFV)	1250mg twice daily
Indanavir /retonavir (ID/R)	400mg/100mg twice daily
Lopinavir/ ritonavir (4V/R)	400mg/100mg twice daily
Saquinavir/ritonavir (SQV/R)	100mg/100mg twice daily

LIST OF CURRENTLY APPROVED ARVS

A. NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI'S)

1. Abacavir
2. Didanosine
3. Emtricitabine
4. Lamivudine
5. Stavudine
6. Tenofovir
7. Zalcitabine
8. Zidovudine

B. NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

1. Delavirdine
2. Efavirenz
3. Nevirapine

C. PROTEASE INHIBITORS

1. Amprenavir
2. Atazanavir
3. Fosamprenavir
4. Indanavir
5. Ritonavir

6. Lopinavir + ritonavir

7. Nelfinavir

8. Saquinavir

D. Fusions Inhibitors

1. Enfuvirtide

Adapted from: Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents developed by panel on clinical practice for treatment of HIV infection, convened by the department of Health and Human Services USA October 29th, 2004.