REVIEW ARTICLE

Challenges if HIV Treatment in Resource-Poor Countries: A Review

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Abstract

Background: *The human immunodeficiency virus/acquired immunodeficiency syndrome pandemic have posed a significant public health challenge to the global community. Massive therapeutic interventions with antiretroviral drugs are being undertaken, yet problems and challenges exist. This review examines these problems and challenges as they affect the treatment of HIV infection in resource-poor countries such as Nigeria.*

Methods: *The information was sourced from relevant literature using human immunodeficiency virus/acquired immunodeficiency syndrome journals, textbooks and Websites on human immunodeficiency virus/acquired immunodeficiency syndrome, highly active antiretroviral therapy, resource-poor countries as key words.*

Results: *Several studies have shown that the advent of highly active antiretroviral therapy in 1996 has significantly reduced morbidity and mortality among people living with HIV/AIDS (PLWHA). But in resource-poor countries, initiation and maintenance of highly active antiretroviral therapy has been associated with many challenges and problems such as: poor infrastructural base for the control programs; irregular or non availability of drugs; poor drug adherence; co-morbidities and opportunistic infections/malignancies; drug toxicities; drug/food and drug/drug interactions; laboratory monitoring of viral load; CD4 cell counts; full blood counts; electrolytes, kidney and liver functions.*

Conclusion: *The review has shown that the solution to the pandemic lies in a multi-sectoral and holistic approach involving International and local agencies, and communities.*

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Introduction

Globally the HIV prevalence has reached pandemic proportions with sub-Saharan Africa accounting for about 25 million of the total 40 million people living with HIV/AIDS (PLWHA) as at 2006[1]. More than 60% of these infected people are in the age group 15-49 years. In Nigeria the adult prevalence had increased from 1.8% in 1991 to 4.5% in 1995, and 5.8% in 2001 before dropping to 5.4% in 2003 and 4.4% in 2005[2].The fight against HIV/AIDS poses enormous challenges worldwide, generating fears that success in its control may be too difficult or even impossible to attain[3]. However, the advent of highly active antiretroviral therapy (HAART) in 1996 has significantly reduced morbidity and mortality, prolonged life expectancy, and improved quality of life among PLWHA[4]. HAART has also been effective in the prevention of mother-to-child transmission of HIV (PMTCT)[5].

The Goals of Antiretroviral Therapy

The goals of antiretroviral therapy (ART) are to provide optimal and individualized treatment for HIV-infected people at all stages of the disease, and in the process reduce the infectiousness of these individuals. These goals are conceptualized in five ways[6] thus ; the prevention of disease progression, prolongation of life and improvement in quality of life (clinical goals); the greatest possible reduction of the viral load to below detectable limits, preferably to < 50 copies per ml of blood (virologic goals); restoration of the immune system both in quantity (normal CD4+ cell counts) and in quality (normal cell mediated functions) (immunologic goals) ; rational sequencing of drugs in a fashion that will achieve clinical, virologic, and immunologic goals while maintaining treatment options, minimizing drug toxicities and maximizing adherence to therapy (therapeutic goals);and lastly reduction of HIV transmission (epidemiologic goals).

In pursuance of these goals, HAART[7] which involves the combination of three or more drugs from at least two different groups or classes are used so that the drugs can act on at least two different points in the life cycle of the virus. The introduction of these drugs, and their widespread use in the developed countries of Europe and America, has changed the gloomy picture of

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HIV/AIDS in these developed economics where the incidence of AIDS decreased from 30.7 to 2.5 per 100 patient years with attendant improvements in the quality of life of the patients[8]. But this is not the picture or situation in Africa. In this continent, especially sub-Saharan Africa, the disease is still on rampage, maiming and killing majority of the workforce and leaving many children as orphans[9]. This situation is consequent upon many factors some of which are discussed below.

Some Benefits of HAART.

HAART has become the standard of care for treatment of HIV infection and has significantly reduced morbidity and mortality among PLWHA as well as prevention of mother-to-child transmission of HIV[10]. It has also created a major incentive for people to participate in voluntary counseling and testing with the knowledge and belief that uninterrupted HAART prevents progression of HIV infection to AIDS and therefore reducing stigmatization[11]. Fear, ignorance and confusion about the infection and its treatment are being replaced by optimism and positive living when PLWHA, their spouses, families, support groups and communities observed the reduced morbidity and mortality and improved quality of life associated with HAART[12]. The massive scaling up of the Nigerian national ARV programs with support from the 3 by 5 Initiative of the World Health Organisation (WHO) [13]; the Global Fund to Fight AIDS, Tuberculosis, and Malaria[14]; the World Bank[15]; and the United States President's Emergency Plan for AIDS Relief (PEPFAR) [16] has ensured the availability of ARVs as well as the provision of ancillary laboratory services both for diagnostic and monitoring purposes at little or no cost to the patients.

Clinical Eligibility Criteria for Initiation of HAART in Resource Limited Settings

Until 2005, only 5% of the over six million people who required ART in resource limited countries could have access to the antiretroviral (ARVs) [17]. Between 2003 and 2005, these numbers increased three-fold, mainly from the massive scaling up of programs supported by the 3 by 5 Initiative of the World Health Organisation (WHO); the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the World Bank; and the United States President's Emergency Plan for AIDS Relief (PEPFAR). In Nigeria with a seroprevalence of 4.4% in 2005 and about 800,000 people in urgent need of ART, fewer than 250,000 adults and children were yet to access these drugs by 2006[18].

In developing countries, clinical eligibility criteria for ART have varied based on several factors. These factors include patients' educational and socio-cultural background, lifestyle and readiness to take ART regularly for life, WHO clinical staging, baseline CD4+ cell count, total lymphocyte count (in the absence of CD4+ cell count) and hemoglobin concentrations, co-morbidities (viral hepatitis, tuberculosis etc.), childbearing potential and HIV RNA levels (viral load) [19].

The WHO 2002 guidelines for initiation of HAART in resource -poor countries have been modified to include[20]:

- Patients with CD4+T lymphocyte counts equal to or less than 200 cells/mm^3 irrespective of WHO clinical staging;
- Patients with WHO stage 4 disease (AIDS defining illness), irrespective of CD4+T lymphocyte count or total lymphocyte count;
- Patients with WHO clinical stage 3 disease (symptomatic HIV) with CD4+ T lymphocyte counts of less than 350 cells/mm^3
- Patients with WHO clinical stage 1 or 2 disease with CD4+ lymphocyte counts of less than 200 cells/mm^3
- Patients with WHO clinical stage 2 or 3 disease with total lymphocyte counts of = 1,200/mm^3 and hemoglobin of = 10 g/dl (when CD4 count is unavailable).
- In these countries, assessment of HIV viral load is not considered essential for determining the need for therapy. However, especially in developed economics, ART can be initiated at viral load above 30,000 copies/ml or > 55,000 copies/ ml by branched DNA or RT-PCR respectively, irrespective of CD4+ lymphocyte counts[21].

Choice of Antiretroviral Regimens in Resource -Limited Settings

In January 2002, the Nigerian Government launched a National ARV program under the WHO 2002 guidelines for initiation of HAART in resource poor countries. The guidelines recommended a protease inhibitor-sparing ART consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitors (NNRTI) as first line regimen. In Nigeria today, most of the government and non-governmental assisted ARV drug programs are based on the preferred first-line regimen-: Two NRTIs (zidovudine or stavudine + lamivudine) + one NNRTI (nevirapine or efavirenz) [22]. The availability of cheaper generic ARV drugs, in contrast to the costly branded ones, have enabled many developing

countries to initiate national ARV program and to add alternative first- line regimens, based on:

(i) Two NRTIs e.g., abacavir (ABC) + lamivudine (3TC) or emtricitabine (FTC); plus one NNRTI e.g., nevirapine (NVP) or efavirenz (EFV)[23] or
(ii) One nucleotide reverse transcriptase inhibitor (NtRTI) e.g., tenofovir disoproxil fumarate (TDF); plus one NRTI (3TC or FTC), plus one NNRTI (NVP or EFV)[24,25].

These ARVs are a new set of drugs with various degrees of potencies and toxic or side effects and their extensive use are expected to present new clinical problems for the patients and health care providers[26, 27]. Therefore, these regimens were chosen as first-line for developing countries because of their potency and durability. Other considerations were: their low pill burden; minimal food requirements and refrigeration storage needs; co-formulations with high mutational thresholds; once or twice daily oral dosing; good tolerability; high resistance profile; good pharmacokinetic profile; minimal toxicity and cost[28].

Based on a review of data from a number of studies[29], the globally preferred initial HAART combinations for adults are: EFV in combination with 3TC and either ZDV or d4T, or TDF; or Ritonavir boosted Lopinavir (LPV/r) in combination with 3TC and either ZDV or d4T. Recently, however, clinicians have been advised to avoid d4T as a first-line therapy or alternatively give the lower dose of 30mg irrespective of patients' weight, because of its long-term cumulative toxic effects[30].

Challenges of ART maintenance in Resource-Limited Settings

HIV specialists have estimated that 10 to 60 years of sustained and uninterrupted ART using current protocols might lead to eradication of the virus in an individual[31], but many workers think that this may be a mirage, because even in developed economies where there are now many effective HAART regimens for the treatment of HIV infection, there are many problems associated with the ARVs and the current ART protocols[32]. First, current ARVs do not cure HIV infection and therefore the drugs must be taken for life[33]. Second, the current ART has many risks and limitations. The complexity of the treatment regimen makes it difficult for the uneducated to comprehend[34]. In sub-Saharan Africa and other developing countries, socio-cultural beliefs and practices some of which inadvertently encourage the transmission and spread of HIV[35], low literacy level[36], unawareness, outright rejection /or poor understanding of the pandemic[37], poverty[38], diseases, none or poor adherence to antiretroviral therapy[39], all of these contribute to poor treatment outcomes or failures. The cost of the drugs, non-availability or irregular supply of potent antiretroviral drugs and poor storage facilities pose major financial challenges[40]. The lack of an adequate health infrastructure, insufficient human resources and official apathy create serious obstacles to laboratory monitoring of diseases and providing ART in an effective, durable, and sustainable manner[41,42].

Early and delayed adverse effects such as gastrointestinal disturbances, metabolic disorders, mitochondrial toxicities, peripheral neuropathies, and numerous organ-specific adverse reactions are continued concerns. The scope of these adverse effects is quite wide and broad and our understanding of their pathogenesis and clinical presentations continue to evolve[43]. Unfavorable interactions have been shown to occur among the antiretroviral drugs and between them and other drugs given for treatment of opportunistic infections, complications of the disease and other co-morbidities[44]. Drug resistances of various forms (mono-, dual-, triple, multi-and cross-) occur for various reasons, foremost being poor adherence to therapy[45,46].

For these reasons, it is widely accepted that current treatment approach is incapable of eradicating HIV completely from the blood, even when the plasma viral load is undetectable with current technological means. This is said to be partly due to the persistence of latently infected resting or memory CD4+ cell populations in lymph nodes, skin and glia tissues which rapidly repopulates the plasma at the slightest opportunity with consequent rebound viremia[47]. It is also thought that prolonged suppression of the viral load by antiretroviral therapy impairs the development of HIV specific immune responses because of persistent sub-optimal antigenic stimulation leading to rapid rebound of plasma viremia when treatment is interrupted[48]. This phenomenon has been confirmed by a study which demonstrated viral replication in the semen of 23% of patients on HAART[49].

Other Challenges and Problems

Drug toxicities

Toxicities or side effects caused by ART can be classified into three broad categories[50].

First category are mild and transient symptoms such as headaches, gastric upset ,nausea, fatigue, mild

rash(without constitutional symptoms) and the central nervous system (CNS) disturbances seen with EFV. These often require patient assurance that symptoms are common and will decrease over time. ART interruption is seldom indicated in this condition. Second category symptoms are more severe and often respond to some medical intervention. ART interruption is usually not indicated and often symptomatic treatment will suffice. These symptoms include more severe headaches, severe gastric upset with nausea and vomiting, and peripheral neuropathy, not incapacitating or interfering with daily activities of living. In the third category, symptoms are so severe that ART must be stopped and replaced by alternative drugs. These symptoms include anemia (hemoglobin <7.5 gm/dl or a rapidly falling hemoglobin that drops by 2 gm/dl from baseline) as can occur with the use of ZDV; nausea with severe discomfort and minimal intake of drugs for 3 or more days, vomiting severe enough to lead to dehydration or inability to ingest food and drugs for 24 hours, severe headache not responsive to non-narcotic analgesics, fatigue reducing activity by more than 50%, hypersensitivity reactions and grade 3 hepatotoxicity or a 5- fold increase in level of transaminases above the upper limit. ABC and NVP hypersensitivity reactions belong to this category.

ABC hypersensitivity which occurs in 3-8% of patients can be fatal if patient is re-challenged with the drug[51]. The symptoms include shortness of breath, cough, fever, aches, fatigue, lethargy, body swelling, abdominal/stomach pain, diarrhea, nausea, malaise, muscle or joint aches, numbness, sore throat and rash[52].

Severe NVP hypersensitivity reactions occurs in the form of Stevens-Johnson Syndrome with severe erythema multiforme,urticaria,desquamation of skin, skin blistering and sloughing, exfoliative dermatitis ,anaphylaxis, mucous membranes involvement, angioedema ,and cracked/fissured lips. Systemic signs include body aches, arthralgia, myalgias, fevers, lymphadenopathy and significantly elevated hepatic transaminases, or frank fulminant hepatitis. These reactions can occur in up to 20% of patients and usually in the first 6-8 weeks of therapy, especially if initiated in women and men with CD4 count >250 cell/mm^3 and >400 cells/mm^3 respectively[27, 53].

Therefore, NVP should be avoided in these patients, and in the absence of facilities for CD4 cell count, should be initiated at a lower dose of 200mg per day for the first 2 weeks, so that if there is no hypersensitivity reaction, the dose is increased to 200mg twice daily. Once this condition occurs, all ART are stopped and patient is treated with intravenous fluids, high dose prednisolone and antihistamines. On recovery, ARV drugs are re-introduced but without NVP which must never be re-introduced.

Anti-retroviral Toxic Neuropathy (ATN) also called ARV-associated distal symmetrical polyneuropathy (DSP) is caused by the dideoxynucleoside NRTIs such as d4T[54], didanosine (ddl)[55], zalcitabine (ddc)[56] and occasionally 3TC[26]. The frequency is 5-24% and is dose related, occurring more in patients with advanced HIV infection ($CD4^+$ count less than 200 cells/mn^3), or who have previously experienced peripheral neuropathy either clinically or sub-clinically before initiation of anti-retroviral therapy . The clinical features are indistinguishable from those of HIV-associated DSP, but the onset of symptoms may provide useful information about the aetiology. This is because AIDS-related DSP may take months to years to develop while ATN tends to evolve more rapidly within a week to six months of therapy and usually resolves if the drug is withdrawn, although recovery may be generally slow. Occasionally, symptom intensification lasting four to eight weeks may occur before eventual improvement. Combination therapy with stavudine and didanosine or zalcitabine when given at lower dosages to patients with baseline CD4+ > 400 cells/mm^3 or with no prior history of ARV therapy appears not to increase the risk of ATN[57.] Management of ATN requires dose reduction or substitution to a less neurotoxic drug without sacrificing virologic control. In cases in which alternative non-neurotoxic ARV agents are not available due to resistance or toxicity, and substitution is not possible without jeopardizing virologic control, symptomatic analgesic treatment while continuing ARV may be appropriate.

Drug-drug Interactions

The pharmacotherapy of HIV infection remains a challenging, long-term undertaking. The use of drugs that may have specific food and pH requirement, for optimal absorption, and that may be substrates, inhibitors and inducers of drug metabolism, yields an environment that is among the most complex in contemporary therapeutics[58]. Available ARV options for HIV-infected person who is receiving tuberculosis therapy with a Rifampicin- based regimen are problematic and limited[59]. Concomitant use of rifampicin with the protease inhibitors (PIs) is contra-indicated because significant reductions in PI concentrations occur as a result of rifampicin CYP450 enzyme induction in the liver[60]. To date, attempts to overcome rifampicin enzyme induction with increased doses of PIs

and/ or ritonavir have not been successful in the case of atazanavir/ritonavir (ATV/R) or have been associated with high rates of hepatotoxicity, as seen with Saquinavir/ritonavir (SQV/r) and LPV/r[61, 62]. Therefore either an NRTI-only regimen or an EFV- based regimen is considered the best ARV option in this setting[59]. Another option is the use of rifabutin with NNRTIs and PIs in patients co-infected with HIV and tuberculosis. Rifabutin is metabolized by hepatic CYP3A enzyme which is induced by EFV but inhibited by delavirdine (DLV) and PIs. As a result, rifabutin's dose has to be reduced if it is used with delavirdine or PIs and increased if it is used with EFV. Rifabutin is not commonly used because of this pharmacokinetic complexities[63].

The PIs have some other limitations associated with their use. To be more effective, most PIs will need to be combined with ritonavir (also a PI) for pharmacokinetic enhancement[64]. This increases the pill burden, cost and side effects. Some of these drugs also require refrigeration storage. These requirements are impediments to effective ART in developing countries with little or no electricity supply and/or refrigeration storage facilities[65].

Antiretroviral treatment failure

The WHO defined antiretroviral treatment failure in terms of virologic failure, immunologic failure and clinical failure. Virologic failure is defined as failure of viral load (VL) to decrease by 1.5 to 0.7 $\log_{10}$ c/mL within 4 weeks, or to reduce <10000 c/mL after 16 to 24 weeks or < 50 c/mL by 4 months of continuous ART[66] . Immunologic failure (or CD4 cell count failure) is a confirmed 50% fall of CD4+ cell count or a 5 % fall in CD4+ percentage, from on-therapy absolute CD4+ cell peak level or fall to baseline CD4+ cell count ,or failure of CD4+ cell count to rise above 100/mm^3 without an identifiable medical cause to explain the low CD4 cell level . It has also been arbitrarily defined as failure of the CD4 count to increase 25-50/mm^3 in the first year of HAART[67]. Clinical failure is defined as occurrence or re-occurrence of an AIDS-defining opportunistic infection or malignancy in the presence of more than 6 months of regular antiretroviral therapy[68]. VL, CD4 cell level and clinical stage of HIV are interrelated in many ways. Late stage (stage IV) HIV disease characterized by VL > 10,000 c/mL and CD4 count < 200 cells/mm^3 is associated with the development of opportunistic infections, tumours, wasting and neurologic complications. Long-term studies show that virologic failure will eventually lead to immunologic and clinical failures, because sustained levels of viremia > 10,000 copies/mL is associated with clinical progression and rapid CD4+ cell decline[69, 70].

Many factors are responsible for ARV treatment failures in resource poor countries. First many patients present late at the AIDS stage of the disease with multiple co-morbidities (tuberculosis, anemia, malaria, malnutrition, hepatitis etc.) requiring ingestion of many drugs. The attendant high pill burden and possible costs, frequent dosing schedule, drug interactions and toxicities may cause treatment interruptions and affect adherence[39]. Second, many patients travel long distances to be able to access HIV care and support, including ART. Financial constraints, unavailability of good and quick means of transportation, inconvenient clinic appointments and long queues at consulting/pharmacy rooms contribute to irregular clinic attendance and consequent drug pick-up failures[71, 72]. Third, initiation of ART, without adequate counseling and education about the disease and its treatment, including opportunistic infection prophylaxis and treatment, is associated with poor adherence and treatment failure. Failure to correct false cultural beliefs about the disease or to reduce its associated stigmatization, poor family and social support systems, emotional instability and high risk lifestyles are additional factors[73, 74].

THE WAY FORWARD

Although many developing countries have adopted various programs to tackle the HIV/AIDS crisis, these programs are yet to achieve stated objectives because they are tailored toward the approaches dictated by the WHO and UNAIDS and not to the peculiarities of each country[75]. Lack of strong political will and response to the HIV pandemic plagues these countries, many of which lack policies that ensure women's equal access to critical prevention and care services or legal measures to prohibit discrimination against PLWHA. Less than 50% of these countries have adopted comprehensive workplace policies addressing HIV/AIDS. Only 40% have a national AIDS monitoring and evaluation plan, yet less than 25% have a national AIDS monitoring and evaluation budget[76].

The solution to the pandemic lies in a multi-sectoral/ holistic approach with interconnectivity and partnerships between the International Agencies [the World Bank, WHO, Joint United Nations Program on HIV/AIDS (UNAIDS), United Nations Population Fund (UNFPA), etc], National Agencies [National Action Committee on AIDS (NACA), National AIDS and STD

Control Program (NASCP), etc], Civil Society Organizations [Society for Women and AIDS in Africa, Nigeria (SWAAN), Network of people with HIV/AIDS (NEPWHAN),etc], local communities, the private sector and individual support groups. These partnerships are expected to lead to a marked increase in international resources available for the AIDS response as well as the strengthening and broadening of national and local response to the HIV/AIDS program with attendant progress in strategies, policies, legislation, action, faith-based leadership, and civil society and community mobilization.

The components of the health sector response should compose of the following:

(i) Informed policy and strategic development. This involves establishing or/and strengthening epidemiologic and behavioral surveillance for HIV and other sexually transmitted infections (STIs); elaborating plans to generate resources; strengthening accountability and monitoring systems for both human and financial resources; countering the stigmatization and discrimination of PLWHAs; reviewing policies, laws, and regulations pertaining to the HIV/AIDS programs such as legal reform advocacy and legal aid for PLWHAs; mobilizing communities, non-governmental organizations, PLWHAs, vulnerable groups, and the business sector through mass media engagement.

(ii) Health standards and health systems. This should involve setting and promoting national standards for the public, private, and community-based delivery of HIV/AIDS prevention, health promotion, and treatment, support and care; building capacity and strengthening health systems; promoting universal safety precautions; and ensuring the safety of blood and blood products.

(iii) Prevention and health promotion. This entails providing support for the development of broad-based programs to educate the general population about HIV/AIDS; promoting harm reduction, and safer and responsible sexual behavioral and practice (e.g., condom use promotion); and targeting interventions to high-risk groups, including counseling and testing.

(iv) Treatment. This incorporates expansion of access to antiretroviral drugs; prevention of mother-to-child transmission of HIV; increasing access to services to diagnose and manage STIs and TB; and providing a continuum of care from home to health facility.

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