Management of Human Immunodeficiency Virus (HIV) Infection in Adults in Resource-Limited Countries: Challenges and Prospects in Nigeria.

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SUMMARY

Nigeria has an HIV seroprevalence of 5.0% with an estimated 3.5 million infected persons. By June 2005, an estimated 28 – 48,000 or 4 – 8% of those requiring Anti-Retroviral Treatment (ART) receive it through various means and support. It is targeted that 350,000 and 1 million persons will be on ART by 2006 and 2009 respectively. Clinical studies on ART have demonstrated virological, immunological and survival benefits comparable to those reported in the developed world. Situation analyses and audits in the country have shown promising and comparable findings to results elsewhere. They have also identified areas of potential concern – rational use of ART, adherence and monitoring. As ART scale up is ongoing there is need for continued technical support, laboratory standardization, commodities management / supply and training of health care workers. Simple guidelines and algorithms for ART, care and monitoring to facilitate rapid scale-up should be developed for use in tertiary and non-tertiary facilities in the country. Preventive and ART services should be fully linked. With considerable funding from many sources there is need for good governance, accountability, coordination and continuous provision of resources with cogent targets and objectives in the scale up as we seek to improve survival, quality of life and productivity of patients in Nigeria.

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INTRODUCTION

Human Immunodeficiency Virus (HIV) infection, the cause of Acquired Immune Deficiency Syndrome (AIDS) is an important cause of morbidity and mortality in much of sub-Saharan Africa. Nigeria currently has an estimated 3.5 million People Living With HIV/AIDS (PLWHAs) and a seroprevalence level of 5.0%. The epidemic has grown beyond the high-risk groups to the general population.

In resource-limited settings most interventions for HIV/AIDS are focused on prevention but in the past few years debate has persisted over the introduction and the degree of emphasis appropriate to the different components of HIV care. Since early 2002 the Nigerian Government has commenced Anti-Retroviral Treatment (ART) in 25 health facilities across the country [1]. This was boosted by the World Health Organization's (WHO) parallel initiative in late 2003 to scale up ART delivery through various sponsors to meet the "3 by 5" target of 3 million people receiving treatment by the end of 2005. By June 2005 the estimated number of people receiving ART in sub-Saharan Africa was 500, 000 or 11% of patients needing ART [2].

This review focuses on management of HIV infection in resource poor settings with particular reference to Nigeria. It highlights the problems and prospects of improving and scaling up HIV care in the country.

Anti-Retroviral Treatment (ART) in Adults

Concerns about the expansion of ART have revolved around the practical challenges of implementing treatment programmes, the high cost of drugs, limited capacity for monitoring and the potential development of drug resistance as a consequence

of poor compliance coupled with negligible improvements in survival. Proponents of ART scale up have invoked human rights arguments, challenged the relevance of cost-effectiveness analyses, expect stigma reduction, improved survival, quality of life and economic productivity and increased uptake of voluntary testing with widespread ART use. However, clinical studies of ART in resource-poor settings have demonstrated virological, immunological and survival benefits comparable to those reported in the developed world [3].

The Nigerian Government commenced using a combination of generic forms at subsidized cost targeting 10,000 adults and 5000 children. By 2004, 14,000 adults were on ART in the 25 centres in 19 out of 36 states and the Federal Capital, Abuja [4]. By June 2005, WHO estimated that the total number of people receiving ART in Nigeria was 28,000 – 48,000 or 4 – 8% of patients needing ART [2]. Reassuringly a recent trial in Cameroon of a fixed-dose generic Highly Active Anti-Retroviral Therapy (HAART) regimen similar to the combination used by the Nigerian Government (nevirapine, stavudine, lamivudine) found 80% of patients had undetectable viral load at 24 weeks even though 92% of participants had AIDS at the beginning.

The probability of surviving and being free of new AIDS-defining events was 85% [5]. Studies have shown median increase in CD4 cell counts ranging from 75 – 245/μL, reductions in viral loads ranging from 1.6 – 3.3 log copies/ml for treatment naïve patients on HAART [5 – 10]. These benefits are associated with increases in median survival gains. In Brazil dramatic improvements with median additional survival gains of 40 months was noted for those diagnosed in 1996 when HAART was introduced compared to those not on ARV managed earlier [11].

Lessons from ART Clinical Audits (Table 1; Figure 1)

An ongoing unpublished audit of patients (n = 274) on the Nigerian Government sponsored ART in Kano found that a fifth of patients were lost to follow up six months [12]. Reasons for loss to follow up were unknown but likely due to mortality, relocation,

cost of ART laboratory monitoring tests, voluntary ART stoppage and debilitating inter-current illnesses with poor support. However, the median follow-up is similar to the 6 – 20 months found in five African countries although the onset of the ART in Kano spans longer than in these studies [5 – 10]. Information on adherence, monitoring test results including CD4 cell counts and adverse drug reactions was lacking or incomplete. Similar findings were broadly noted in an assessment of a pilot ART programme in Uganda [10]. Independent indicators of initiating ART in HIV infected patients are significant symptoms, CD4 cell count of < 350/cmm, (or, if not available, lymphocyte count below 1200 per cmm with symptomatic disease) or high viral load [13]. However, only 4 of the 25 national centres initiated ART based on viral load testing [1]. Low cost, low technology assays to measure and monitor HIV load such as the Cavidi RT assay are being explored for use in resource-limited countries. In few patients (4%) ART was started without CD4 cell counts. Given the relatively high proportion of persons with high CD4 cell counts who were started on ART, the limited use of co-trimoxazole prophylaxis and under recognition of adverse drug reactions (ADR) from the audit indicates the need for continued education of health care givers about ART. The modular training initiative should be used to rationalize use of ARVs in patient management practices. To facilitate this, the WHO has released guidelines on simplified algorithms for treatment and monitoring to facilitate rapid scale-up of ART in resource-limited settings [2, 13].

The median CD4 cell count gains on initiating ART (Table 1) is higher than figures cited in studies which used flow cytometry [5 – 10]. It is reassuring but not easily explained, though manual coulter or dynabeads methods of counting CD4 cells are laborious, more prone to inaccuracy at higher cell counts and has poor correlation (r = 0.45) with values obtained by flow cytometry [14]. However, several groups have found good correlation between CD4 cell counts measured by coulter (manually) or by dynabeads with flow cytometry (r = 0.90 – 0.93) [14 – 17]. Figure 1 shows the two year progression of CD4 cell counts in patients on ART. Flow cytometry was started 3 – 4 months ago at

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Table1: Findings in 274 HIV infected patients on ART* in a clinical audit in Kano.

Parameter	Value or proportion (%) (N = 274)
Follow-up (mths) median [range]	17.5 [1 – 38]
Patients with follow-up < 6mths	54 / 274 (19.7%)
Pre-therapy #CD4 cells/cmm	
median [inter-quartile range] *(n = 263)*	219 [131 – 320]
patients with pre-therapy #CD4 cells/cmm = 500/cmm	41 / 263 (15.6%)
#CD4 cells/cmm gain at ~24 wks over pre-therapy values	
median [inter-quartile range] *(n = 101)*	+ 348 [221 – 602]
Proportion with inter-current illness(es)	122 / 241 (50.6%)
Proportion with adverse drug reaction (ADR)	12 / 246 (4.9%)
Proportion on co-trimoxazole prophylaxis	46 / 268 (17.2%)

* 95.1% of patients were on nevirapine, stavudine, lamivudine combination. This combination is charged at N1000 per month's course. In the 38mths of the program there was a 3mths period when drug supply was erratic.
 # CD4 cell counts was done using Manual / microscopic CD4 cell count (Coulter) and Dynabeads (Dynal) according to availability. Patients were charged N3000 per test

Figure 1. Two year progression of CD4 cells in 263 patients in Kano
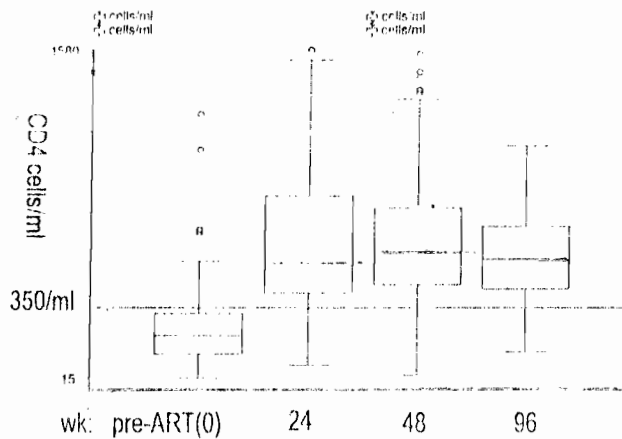
Fig 1:

President's Emergency Plan For AIDS Relief AIDS Care and Treatment in Nigeria (PEPFAR / AC-TION) sites free of charge. It should be used widely in state or zonal centres. Taken together, this means whichever method is used there is need for continued technical support, quality control and quality assurance programmes in laboratories.

Monitoring

The total lymphocyte count is an imperfect predictor of CD4 cell counts. In a study of 2777 HIV seropositive persons in South Africa, the overall correlation between CD4 cell and total lymphocyte count was only modest (r = 0.70) [18]. In Nigeria a study of 32 adults with HIV infection who commenced ART found only a very weak correlation between the parameters (r = 0.25) [19]. However,

given the laboratory infrastructural deficiencies especially in non-tertiary health facilities total lymphocyte count can be used as a surrogate marker for absolute CD4 cell counts [13]. Our experience from preliminary analyses suggests simple measurements like changes in weight and haematocrit fairly mirrors CD4 cell changes. The combination of a modified WHO clinical staging system for HIV infection with haematocrit was demonstrated to predict CD4 cell counts of < 200

cells/cmm in Brazilian patients [20]. Their potential in conjunction with clinical staging, performance status and total lymphocyte count for monitoring patients on ART should be explored for use in non-tertiary health facilities. In tertiary PEPFAR/ACTION sites CD4 counts and laboratory monitoring tests are now offered free and should be used.

Adherence

Adherence is an important determinant of survival and is challenging in resource-poor settings where ARVs may be used without appropriate counselling or monitoring tools [21]. However, reports of adherence levels above 90% in Senegal and South Africa are encouraging [22, 23]. The Federal Government and PEPFAR charge N1000 per month for ART in adults but drug costs are important determinants of non-adherence with a study in Botswana estimating that adherence would rise from

54% to 74% if drugs were provided free [24]. It is hoped drugs will eventually be free. Sub-optimal adherence to ART is likely to result in the transmission of drug resistant virus strains within the community [21]. Despite the imperfections cited earlier several explanations can be adduced for failure of a sustained CD4 cell rise in Figure 1, though possibility of drug resistance reaffirms the need for rational ARV use, provision of second line and salvage alternatives as well as the need for resistance surveillance.

A study in Uganda found higher rates of resistance with poor adherence and dual therapy (especially to lamivudine) than in those who received HAART [10]. Other factors that affect adherence should be studied locally. Directly Observed Therapy Short course (DOTS) has been suggested

as a method for delivering ART and improving adherence, although it has limited success for tuberculosis in much of Africa with success rate of 75 – 79% in Nigeria [25, 26]. Home-based care and DOT should be considered in certain circumstances. Patient-focused, provider-focused and regimen-focused interventions should be studied and explored to improve adherence to ART in the country.

Management of Opportunistic Infections

In Nigeria, HIV is an important cause of mortality in hospitalized patients admitted to adult medical wards. For instance at AKTH in Kano, 30 – 40% of HIV infected patients die from poorly recognized or managed inter-current illnesses (unpublished) [27]. Common causes of death in hospitalized HIV infected adults in sub-Saharan Africa (Cote d'Ivoire, Zaire) include tuberculosis (38 – 41%), bacterial pneumonia (30 – 34%), cytomegalovirus (13 – 18%), cryptococcosis (3 – 19%), bacteraemia (16%), kaposi sarcoma (9 – 16%), cerebral toxoplasmosis (11 – 15%), non-specific enteritis (10%), etc [28, 29]. In Zaria, Nigeria, tuberculosis and acute bacterial infections accounted for 29% and 20% respectively in HIV infected hospitalized adults [30]. Given that HIV infection *per se* rarely kills, the capacity of health facilities to recognize, diagnose and manage opportunistic infections should be strengthened in addition to ART provision.

Faced with limited resources, the best framework for decision making is one that benefits the individual HIV infected patient and other people including those not infected with HIV. The clearest example of a high priority public intervention against opportunistic infection is probably the diagnosis, treatment and prevention of tuberculosis. Thus, in such settings essential packages for care should be provided. Essential drugs list for HIV/AIDS should be formulated for use especially in non-tertiary settings in the country. Such a list should contain – antituberculosis drugs, cotrimoxazole, ketoconazole (or fluconazole), metronidazole, broad-spectrum antibiotic (e.g. ampicillin), nystatin, gentian violet, hydrocortisone cream, codeine, paracetamol, aspirin, chlorpromazine, diazepam, multivitamin, calamine lotion, etc [31]. This should not be confused

with the Essential Medicine List for Nigeria which was updated in 2003 and consists of 8 ARVs; didanosine, lamivudine, stavudine, zidovudine, efavirenz, nevirapine, indinavir, nelfinavir and fixed dose combination of lamivudine, stavudine and nevirapine. With the widespread limitations to diagnose opportunistic infections aetiologically, care approach should be syndromic as recommended by WHO and adopted in many sub-Saharan African countries notably Botswana [13, 32].

Rather than addressing tertiary settings solely, national guidelines should include management protocols for common syndromes and presentations [32], like the ones developed in Kano. These should incorporate limited number of laboratory tests.

Linking Preventive Programmes to ART

It has been shown that even with widespread use of ART the probability of epidemic eradication is high (0.85) only if risky sexual behaviors decrease [33]. Epidemiological analyses and modeling suggest that if the successes achieved in some countries in prevention of transmission can be expanded to a global scale by 2005, about 29 million new infections could be prevented by 2010 [34]. It is therefore necessary to strengthen linkages between ART and prevention programmes: Voluntary Counseling and Testing (VCT), Sexually Transmitted Diseases (STD) programmes, Tuberculosis (TB) services, Prevention of Mother-To-Child Transmission-Plus (PMTCT-Plus), etc. A large randomized trial in Kenya, Tanzania and Trinidad demonstrated 32% reduction (p <0.0001) in such risky behaviors- the proportion reporting unprotected sex with a non-primary partner in VCT group compared with the control group affirming the potential role of VCT in reducing transmission [35]. Two large intervention trials in Mwanza, Tanzania and Rakai, Uganda on syndromic and mass management of STDs as a prevention tool for HIV infection found discrepant results [36, 37]. The intervention in Tanzania reduced HIV incidence by an estimated 42% while it showed little impact in Uganda [36, 37]. Possible explanations for these findings include maturity of the epidemic and the high rate of genital herpes in Uganda, as well as differences in the intervention strategy [38].

However, as STDs are important biological co-factors in the transmission of HIV, STD clinics provide important entry points into ART programmes and the two should be strongly linked within the country. The PMTCT-Plus aims to provide lifetime treatment to mothers and to prevent neonatal transmission [39]. This has been reflected in the recently revised national guidelines. Not only linkage of services is strongly desirable but integration of ART with these aspects of care and prevention should be mandatory wherever possible.

Conclusion, Scaling-up ART and Support

Nigeria has an on-going generalized epidemic and inevitably care will have to be scaled up considerably. It is targeted that 350,000 and 1 million persons will be on ART by 2006 and 2009 respectively (PEPFAR/ACTION). Several organizations including PEPFAR, Global Fund for Tuberculosis, AIDS & Malaria, WHO '3 by 5', World Bank, AIDS Prevention In Nigeria (APIN), Federal Ministry of Health, National Action Committee on AIDS (NACA) etc provide funding and support for these programmes and the ART scale up. Their initiatives are managed in the country by US Centres for Disease Control (CDC), US Agency for International Development (USAID) and others through tertiary institutions like Institute of Human Virology (IHV), University of Maryland, Harvard School of Public Health and Non-Governmental Organizations like Family Health International / Global HIV/AIDS Initiative in Nigeria.

The scale-up calls for appropriate achievable objectives which among others should: strengthen procurement and supply management systems ensuring continuous availability of commodities, diagnostics, drugs and supplies; ensure that health facilities are adequately equipped and personnel possess the knowledge and skills to deliver ART; strengthen systems for monitoring, evaluation and operational research; strengthen the involvement of communities in supporting the provision of ART; develop mechanisms to facilitate access to ART for the poor and vulnerable groups. There should be good management, coordination, accountability and provision of resources in the scale up as we seek to improve the survival, quality of life and productivity of PLWHA in Nigeria.

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