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NIGERIA

A MULTISECTORAL HIV/AIDS RESPONSE AND ANTIRETROVIRAL THERAPY MANAGEMENT IN FEDERAL REPUBLIC OF NIGERIA

A 'care and support' case study

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by

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**INVESTING IN HEALTH FOR
AFRICA'S SOCIO-ECONOMIC DEVELOPMENT**

Summary

President Obasanjo instructed his government in April 2001 to start free ARV administration as part of a comprehensive care programme for the public sector - The Government then requested technical assistance from UNAIDS. The ARV pilot programme has been started and planned as a pilot trial. This trial is guided by a protocol titled:

“An accelerated clinical trial of a combination of stavudine, lamivudine, and nevirapine in the treatment of people living with HIV/AIDS in Nigeria”

It is complemented by a set of case report forms. The objective of the Clinical Trial is:

“To assess the efficacy and safety of the three-drug regimen”

The case study outlines the prospects for a responsible national ART programmes that will fulfil the aspirations of PLWHA for a more abundant life in the country. As such it focuses on the technical and operational dimensions of the programme and the challenges that are faced by African countries in this lone war against HIV/AIDS.

Introduction

Nigeria has launched a comprehensive HIV/AIDS national response based on the HIV/AIDS Emergency Action Plan (HEAP) and an ART programme to 15,000 PLWHA as a special initiative of President Obasanjo following his commitment to the follow up of the **ABUJA DECLARATION ON HIV/AIDS, TB AND OTHER RELATED INFECTIOUS DISEASES**. This came as part of Nigeria's contribution to the national response and along with other activities is budgeted to cost to the tune of USD 57 millions. The case study is based on technical reports¹ of the national response and studies that were commissioned to look at the ARV management in Nigeria immediately after the inception of the programme. The summary presents the processes that led to the initiation of the ARV administration and recommendations to the national ARV Committee, the Health Ministry, and the UN and development partners.

1. The care programme is part of the eight HEAP strategies i.e. promotion of behaviour change, information management, ensuring adequate resources, developing institutional capacity, targeted interventions at vulnerable groups, interventions for the population, care and support for persons infected and affected by HIV/AIDS
2. A crucial measure in the operational development of the programme was the setting up of the ARV Committee, the training of trainers at all levels, the appointment of principal researchers, monitoring team and trial managers, the availability of drugs and capacity building of the 25 teaching hospitals chosen for the task.
3. Recommendations: The ARV Committee may consider synchronizing the HIV drug management guidelines with existing or future regimens in other best practice cases including (1) changing the inclusion criteria CD4 < 200 for asymptomatic patients, and CD4 < 350 for symptomatic patients. (2) Revise the patient information leaflet and informed consent. (3) Select alternative ARVs and recommend procurement of such drugs. (4) Guidelines for paediatric ART (5) The monitoring task force will have to visit all pilot sites. (6) More time to counselling during the recruitment process, to obtain maximum adherence in patients.
4. Government (1) must study conditions for expansion of the programme (2) Provide guidelines for investigators to report all serious adverse events immediately. (3) Establish network of State Coordinators for ARV. (4) Establish email discussion groups for clinicians, ARV Committee (5) Collaborate with PMTCT in VCT, logistics, training and advocacy. (5) Standardize counselling curricula in national workshop. (6) Pharmaceuticals should be encouraged to register their drugs (7) Establish a pricing intelligence committee to monitor ARV prices. (8) Buying TB drugs at lower cost (9) Access the fluconazole donation programme (10) A pilot programme with cotrimoxazole prophylaxis. (11) Introduce health safeguards in the Patents Act.
5. Development partners should strengthen the ARV Unit. The team can start as a small monitoring team in the current clinical trial.

The following parameters will influence the success of a long-term ARV programme: (a) ensuring political will, supported by information, education, communication; participatory approach, human and financial resources development, decentralisation, international partnerships, and Institutional capacity building. On the technical side we need to develop standard therapy guidelines, ensuring a continuum of care, availing cheaper, good quality medicines and diagnostic tests, ensuring strict Adherence by patients, down-referral of stabilised patients to near-by health centres and referral for complications. Collaboration with NGO/CBOs for community home-based care, monitoring and evaluation and operations research is essential for the success of the programme.

Part I

Backgrounder to the National Response and the ART Programme

Nigeria is the most populous African nation with a population of (120.2 million) and an annual growth rate of 2.8%. The country is divided into 6 geo-political zones with 36 states including the Federal Capital Territory, 774 local government areas, and over 250 ethnic groups. The first case of AIDS was formally diagnosed in Nigeria in 1986 and since then there has been a consistent rise in the prevalence of the epidemic from 1.8% in 1993, to 3.8% in 1994 to 4.5% in 1996 and to 5.9% in 1999. It is estimated that 3.5 million Nigerians are already infected with HIV. The highest prevalence is in the age group 19 – 24. These are the productive, reproductive, and economically viable segment of the society.

With 5.8% prevalence of HIV seropositivity reported from the results of the 2001 seroprevalence survey, Nigeria is now on the threshold of the explosive phase of the epidemic. Fortunately, hope has been offered by political commitment expressed at the highest levels with the proclamation of the Presidential Committee on AIDS and the National Action Committee on AIDS to lead a new multi-sectoral response to the epidemic in this country. For an effective and coordinated response, Nigeria has developed the HIV/AIDS Emergency Action Plan (HEAP). The development of HEAP was a critical activity in the resource mobilization and the execution of programmes. HEAP strategies are focused on

- Promotion of Behaviour Change
- Generating and using technical Information
- Ensuring Adequate Resources
- Developing Intuitional Capacity
- Targeted Interventions at youth, to reduce high risk behaviour, empowerment of women to negotiate sex, armed forces and police, prevention of infection through MTCT, commercial sex workers, prisons and immigration, prevention of HIV infection, long distance drivers
- Interventions for the population
- Care and Support for persons infected by HIV/AIDS and a specific TB component of Care and Support for persons infected
- Care and support for persons affected by HIV/AIDS

HEAP sets out the projects and activities to be pursued by the Federal Government of Nigeria over the planning period 2000 to 2003. The terms of reference (TOR) for developing the HEAP evolved from an extensive process of consultation with all stakeholders in a strategic planning process encompassing four major steps

situation analysis, response analysis, action plans and strategic plans and resource mobilization. The activities under the HEAP are conceived as short-term high impact projects, which will feed into a process of medium term planning in the 5 Year Strategic Plan for HIV/AIDS in Nigeria. The first interventions under the new multi-sectoral, participatory response to HIV/AIDS prevention and impact mitigation will be introduced under the HEAP. The HEAP will therefore serve as an important testing ground for deriving best practices, coordinating strategies, high impact responses and as a bridge to the Strategic Plan.

President Obasanjo instructed the Ministry of Health in April 2001 to start a care programme including anti-retrovirals for the public sector. Government then asked technical assistance from UNAIDS. The ARV pilot programme has been started and planned as a clinical trial. This ARV clinical trial is guided by a protocol titled: "An accelerated clinical trial of a combination of stavudine, lamivudine, and nevirapine in the treatment of people living with HIV/AIDS in Nigeria." It is complemented by a set of case report forms (CRF). The stated objective of the Clinical Trial is: "to assess the efficacy and safety of the 3-drug regimen." The trial design, however, does not really allow for conclusions on efficacy, as no control or placebo group has been included. The clinical trial might however provide some data whether the d4T-3TC-NVP combination achieves viral suppression and increasing CD4 counts in the Nigerian setting with different clydes of HIV strains and a different genetic population compared to US or Europe where these drugs have been used before.

The National Anti-retroviral Access Committee ("ARV Committee") was established in April 2001 to advise Government

on clinical matters and to supervise the ARV programme implementation. The Committee consists of clinicians, laboratory pathologists, public health policy makers, researchers, academics, development partners (UN, bilaterals), PLWHA, and Government. The ARV committee meets (bi-) monthly on invitation of Government. Meetings have been sponsored by UNAIDS. The ARV Committee has formed several subcommittees: Policy, Plan of action, Guidelines, Monitoring, and Paediatrics. Other subcommittees can be formed as and when needed. Setting up and rolling out (simultaneously!) both a PMTCT and ARV pilot programme is a big task, and the unit needs urgent expansion. The ARV Committee constitutes the highest level for decision-making, problem solving, and advocacy. The committee meets at regular intervals. There are sub-committees and thematic groups (Legal, Technical, and Advocacy). The ARV committee selected 25 centres for 'the pilot' phase of three months. Drugs were distributed to the 25 centres.

Training: The programme commenced with a training health care providers during the last quarter of 2001. Principal Investigators were briefed and oriented at a meeting in Abuja on the programme. There were 25 of them from the 25 initial facilities. Similarly Pharmacists and laboratory scientists were exposed to minimal training on drug handling, storage, confidentiality, dispensing, and recording. Laboratory scientists were also briefed and oriented on baseline investigations but with emphasis on CD4 counts using Dyna beads technique. An average of two laboratory scientists were trained from each of the centres. Training of staff for the counselling and home based follow-ups is planned. Meanwhile home visits and limited counselling sessions take place in the centres. The plan of action contains lot of capacity building activities for the first year of the programme for different cadres of staff. These include refresher training on HIV management.

Drugs: Although ART have been in the country in private health facilities, prescription and regimens were at the discretions of the attending prescribers. Such drugs are obtained either from some pharmaceutical companies like Pfizer, Glaxo or bought in by private importers. Costs are very exorbitant. Duo-therapy cost as high as 60,000 naira (600 dollars) per month. Examples of such are Combivir, AZT, Indinavir, Efavirens, and Sequenavir. The MOH imported generic drugs from CIPLA and subsequently ROMBAXY. Three drugs were initially imported (Stauvidine,

Lamuvudine and Nevirapine). Following recommendations of WHO/UNAIDS plans are underway to broaden the range to include alternatives in case of resistance or severe side effects. The drugs were distributed to 25 pilot sites for proper distribution and dispensing. An initial stock of dr4ugs for 8,000 treatments was brought in December 2001.

Beneficiaries: Direct beneficiaries are PLWHA (i.e. a person with confirmed HIV infection). The initial inclusion criteria include CD4 \leq 350, viral load greater than 200ml, willingness of Patient to start treatment and a written consent. Initially, cost was not a factor as the government gave the drugs out at no cost to patients Tests were to be paid for by government as well. This will be changed on the expansion of the programme. The initial tests required for inclusion are CD4 count FBC & CXR. During the initial three months, CD4 were done in two designated laboratories, one of which also does viral load while other tests were carried out at sites.

Sites: The initial sites are situated in the six geological zones of log. Principally there are 25 faculties direct supervised by Federal Ministry of Health. NIMA LUTH MILITARY HOSPITAL BENIN T.H UCH, UCTH, UNTH, UITH, JUTH, ABUTH, NIPRD, Gwagwalada National hospital State house clinic UPTH, OPUH, FMC Markurd, FMC, Abeokuta FMC

Monitoring: Monitoring constitutes a vital part of the programme and therefore carried out at various levels. In addition to the continuous site supervision and monitoring by the Heads of the Institutions and the principal Investigators, a dedicated team of monitors was constituted to round the sites from time to time. In addition consultants from WHO and UNAIDS visit the project at intervals to recommend appropriate modifications if any. The ARV committee appointed a team of monitors. They include virologists, clinicians, laboratory scientists, pharmacists, and public health physicians from the Ministry, UN, Universities, and Research institutions.

Principal Investigators: The principal investigators are responsible for supervision at the respective sites. They were initially briefed on the protocol and expectation of the programme. At this level, they will work and hold meetings with the ARV committee to ensure good quality and efficiency in the day to day running of the programmes.

UNAIDS: WHO/UNAIDS fielded a mission at the early stages of the project to assess the conception and make recommendations to the government, ARV committee, UN agencies, PLWHA and the site authorities towards improving the outcome of the programme. WHO fielded another mission from AFRO 3 months after the initial mission to look at the ARV project within the context of care and support for PLWHA. Another mission is scheduled to coincide with the commencement of scaling up process of the programme from 25 to 200 patients per site. The monitoring tools should be modified from time to time based on the dynamics of experience. Development of resistance, rates of toxic effects,

types of availability of relevant drugs and tests as well as government health policies.

Funding and publicity: The President of Nigeria made the initial pronouncement during the Abuja Summit in Abuja that the government will sponsor 15000 PLWHA with full access to drugs. This was followed by series of pronouncements and newspaper publications by the minister for health at intervals and during state/official occasions. The ARV committee has a publicity committee that will feed the public with accurate information.

Part II

Recommendation to enhance the ART Programme

- 1) **Recommendation I: Ask investigators to report all serious adverse events immediately to Government and the ARV Committee.** The "normal" adverse events can be reported on CRF forms, and sent monthly to NASCAP. All serious events and a summary of normal adverse events should also be reported to NAFDAC. 25 pilot sites have been earmarked by Government for the ARV clinical trial. Under the clinical trial conditions set by NAFDAC, each site may recruit a maximum of 25 patients. This means a doctor can expect to see on average only one trial patient per day. In total a maximum of 625 patients can be recruited in the trial. According to the protocol, clinical trial subjects are to be followed-up monthly for a period of 24 months. The follow-up visits, tests, and drugs after the initial three months will have to be paid by the patient. This deviates from the international norm that a sponsor should take care of all clinical trial related costs. Patients get a 2-page information leaflet, which also acts as written informed consent form. This leaflet needs a critical review, as the risks of ART are not objectively portrayed (skin rash the only risk of ART!?), and the objective of the clinical trial is not sufficiently explained. More could also be said about the need for optimal adherence, and patient rights.
- 2) **Recommendation II: Involve more PLWHA in counselling; this could also create job opportunities.** Male condoms are not freely available in health centres but are available at a subsidized price of N10 (USD 0.07) per packet of 4 in the private sector (Gold Circle,

subsidized brand of the social marketing campaign). However, condom use is still low (only 37.7% of men and 20% of women ever used a condom; 1999 Demographic study). Use is increasing slowly. Female condoms are not yet widely available. HIV testing is possible in many health facilities. Rapid tests and Elisa are being used. USD 2.20-3.70 is being charged in health facilities, which run revolving funds to buy laboratory reagents and diagnostics.² Government has agreed to make HIV testing free for PMTCT³. The most common opportunistic infections (OI's) in Nigeria are: tuberculosis, bacterial infections, pneumonia, oral thrush, systemic fungal infections, and chronic diarrhoea. They can in principle be treated in Nigeria's public health system, but drugs have to be bought from the local revolving drug fund, and are often out of stock.⁴ TB-treatment is in principle available at no cost in 21 of 36 States through donor-funded programmes. However, management problems do not always ensure a steady supply of TB drugs.⁵

- 3) **Recommendation III: consider options to buy TB drugs at lower cost from Green Light Committee.** DOTS is in principle being applied for 6-8 months; a cure rate between 65-75% is being claimed. The ARV programme might want to learn from the DOTS efforts to ensure adherence. Fluconazole (Diflucan®, Pfizer) is the drug of choice against Cryptococcal meningitis and oesophageal candidiasis. It has replaced ketoconazole on WHO's EDL due to a better side-effect profile. However, fluconazole is hardly being used in Nigeria due to its excessive cost. Generics are

not yet available. In 2001, Pfizer announced a free donation programme for 50 developing countries, but Nigeria does not yet seem to benefit from this.

- 4) **Recommendation IV: Government to contact Pfizer to access its fluconazole donation programme:** Cotrimoxazol prophylaxis is not yet government policy or standard practice. There is reasonable evidence that cotrimoxazol prophylaxis could benefit HIV+ people. Considering a pilot programme with cotrimoxazole prophylaxis is recommended.
- 5) **Recommendation V: Nutritional care for HIV:** a national nutritional policy has been developed in 2001, and addresses issues on infant feeding and HIV. There are no specific activities yet at health facility level. Breast milk substitutes are not affordable for majority of Nigerians. The community-based care manual "Care for people living with HIV/AIDS" has a small chapter on nutrition. The recommendation advises to consider nutritional activities for PLWHA.
- 6) **Recommendation VI: Strengthen the NASCAP ARV Unit by urgently attaching a HIV-clinician, a training adviser and a pharmacist/logistician** - Standard palliative care is available in some health facilities, but due to the high number, people living with AIDS are often sent home, where NGOs/CBOs or AIDS Support organisations struggle to deliver a form of home-based care. Psycho-social support: few social workers and counsellors probably means that only limited support is available in health facilities. PLWHA needing psycho-social support will need support from their family, neighbours and nearby community. Such support is difficult to obtain if stigma prevails and PLWHA have to hide their status. Lifting stigma and thus enabling psycho-social support by the community will be a crucial role for NGOs, CBOs and AIDS support organisations. With home-based care, this is largely dependent on a locally operating church, CBO, NGO or AIDS support group. Until recently, anti-retrovirals were only available in the private sector at high costs.
- 7) **Recommendation VII: Synchronize the guidelines with existing or future regimens.** "Guidelines for the use of ARVs in Nigeria" were published by NASCAP in July 2001. They offer several treatment options to prescribers, even though there is currently only one standard

regimen available in the programme (d4T-3TC-NVP).

- 8) **Recommendation VIII: Ethics Committee should revise the patient information leaflet and informed consent.** In December 2001, NASCAP developed a "Plan of Action for broad access to ARVs in Nigeria." The overall objective (mission) of the Plan is "To improve quality of life of people living with HIV/AIDS in Nigeria, so that they can meaningfully contribute to sustainable development of the Nation." The plan of action has 2 parts (erroneously called phases; they run concurrently from 2001-2003).
 - a) Phase/part 1 (objective: "**Strengthening the initiative on access to ARV for PLWHA**") lists activities for a total budget of USD 172m. These include advocacy activities for all target groups, cost of expanded AIDS treatment, human resource development, logistics management, expanding participation, resource mobilisation and basic and operational research and monitoring & evaluation.⁷
 - b) Phase/part 2 (objective: "**Capacity building throughout Nigeria**") lists activities for a total budget of USD 5.3m. Capacity building is very important, as nearly all aspects of the ART programme might suffer from weak infrastructures and human resources. NASCAP has in principle access to funds from the HIV/AIDS Emergency Action Plan (HEAP), which has an USD 30m budget for capacity development, and USD 33m for an HIV/AIDS Community Fund. The total budget for 2001-2003 ARV Action Plan (phases/parts 1 and 2) is USD 177m. It is unclear from which donor this budget is sought. About USD 4.3m has been made available from government sources; around USD 3.5m of this has so far been

The advent of new classes of ARV drugs and their use in combination have changed the way people in the world's richest countries think about HIV/AIDS. Although these treatments are not a cure ..., they have dramatically improved rates of mortality and morbidity, prolonged lives, improved quality of life, and transformed perceptions of HIV/AIDS from a plague to a manageable, chronic illness. Unfortunately, most of the (PLWHA) in the developing world do not share this vastly improved prognosis.⁶

spent on buying 8,000 treatment-years of ARVs from CIPLA and Ranbaxy, India. A credit of USD 0.75m is still available. Funding up to USD 31m might be available for "expanding the public sector response" to AIDS in the HEAP. It is recommended to revise the budget after discussing updated Plan of Action.

- 9) **Recommendation IX: Allow the existing pilot sites to expand from 25 to 250 patients, depending on their own capacity.** Prospective patients are expected to arrange for HIV test, CD4 count and blood chemistry tests before being considered for inclusion. The cost of these tests is estimated at N 9,000 - 15,000. In principle, government agrees to reimburse these costs. The current practice results in an additional financial barrier to ART access. Some of the tests being requested in some sites are not very relevant for the protocol (e.g., ECG, X-ray). These tests increase financial burden to patients and add little information to the trial. The ARV Committee trained the principal and co-investigators of 18 sites in a 3 days workshop at NIMR, Lagos. A second batch of health workers of the remaining seven sites was invited to a much shorter 1-day sensitisation workshop at NIPRD. This may have been too short for a new and complicated therapy. A 2-3 day training seems indicated for health workers who want to become involved in HIV/AIDS management. Laboratory staff of 18 sites was trained in CD4 counts and other required clinical trial tests at NIMR. To obtain maximum adherence, more efforts should be put into training of nurses, social workers, counsellors, and even patients! The ARV Committee took the decision for the clinical trial to go ahead. Each pilot site was requested to get local Ethics Committee approval. The issue who will pay for patients after the initial 3-months in the clinical trial might warrant some ethical discussion.⁸
- 10) **Recommendation X: Consider changing the inclusion criteria CD4 < 200 for asymptomatic patients, and CD4<350 for symptomatic patients (stage 3 or 4).** This will allow doctors to get reasonable experience (expected number of contacts per day: 10 as opposed to 1 currently). This protocol change will also need a decision whether this will be seen as an expansion of the existing clinical trial or as a scaled-up follow-up if patients have to pay N 1000/month. The current inclusion criteria are: 100 < CD4 < 400. This is different from current WHO recommendations: 0 < CD4

< 200 (asymptomatic) or CD4 < 350 for symptomatic patients (with AIDS defining illness, stage 3 or 4). The exclusion of patients at highest risk (CD4<100) introduces a bias in the clinical trial results, and could be criticised from a patient rights perspective, as this group needs the ART most.

- 11) **Recommendation XI: Government, ARV Committee and UN Theme Group must pool resources and appoint a small monitoring team.** Pregnancy and active TB are currently exclusion criteria in the clinical trial setup. As these are common conditions in the target group, future ARV guidelines will have to be expanded to cater for these groups. The current protocol can be used in pregnancy, but NVP might have to be changed for efavirenz in case of a concurrent rifampicin-containing TB regimen.⁹ Few counsellors are available in the pilot sites, and counselling capacity is probably insufficient. This might affect negatively on adherence by patients. Hospital budgets are mostly frozen, making it unlikely that hospitals can appoint counsellors as new staff. However, PLWHA might be interested to become lay-counsellors, and assist pilot sites in the recruitment, counselling and supporting on prospective ARV patients. A creative solution is needed how such lay-counsellors could be employed at pilot sites. Clinical trial reporting forms have been designed. NASCAP distributed diskettes with the forms to the 25 centres, and requested pilot sites to print them locally. Completed CRF forms are expected back at NASCAP after the 3 initial months of clinical trial. Data will be computerised by a statistician. The monitoring subcommittee will then analyse the data and make recommendations to ARV Committee.¹⁰
- 12) **Recommendation XII: Establish a media/communication subcommittee; develop a pro-active media strategy; publish pro-active press-releases about the ARV Programme.** A country-wide roll-out can start formally only start after a positive decision by NAFDAC to register the generic ARVs. The registration will also allow the marketing of the generic ARVs in the private sector, and is likely to create a price war. The objective of the 24-month follow-up of the trial subjects is to assess long-term adherence, toxicity, and clinical outcomes. No specific resources have been made available, and given the need to expand rapidly, one wonders whether this phase will produce specific results. An alternative would be to

design a sentinel surveillance structure (linked to the annual ante-natal surveillance?) or monitor specific cohorts of patients more intensely in sites with extra resources (e.g. VL capability). As the clinical trial has started, it is only a matter of time before journalists start writing sensational articles about the trial. As 30 Nigerians die every hour of AIDS, it is quite likely that a trial subject may die during treatment. NASCAP and ARV Committee should take the lead and inform media pro-actively about the clinical trial, the ARV drugs used, the risks and benefits involved, and the future roll-out plans.

13) **Recommendation XIII: ARV Committee to decide on alternative ARVs drugs to be used in the HIV/AIDS Guidelines. Government could then procure such drugs through a limited bidding tender.**

Only one regimen is currently available: 40mg d4T + 150mg 3TC + 200mg NVP. No documentation is available why this combination was chosen. All parties agree that alternative ARVs are needed, as the current regimen will be insufficient.

- a) For light patients (<60kg), a 30mg d4T tablet might be indicated. For TB co-morbidity, nevirapine could be swapped for efavirenz. The current d4T-3TC-NVP regimen could use the following alternatives as a replacement in their class (for individual allergies; not for resistance purposes: that requires a totally different regimen!): zidovudine (AZT) 300mg BD in case of d4T allergies, didanosine (ddl) in case of 3TC allergies, efavirenz in case of nevirapine allergies. HIV experts predict a 60% virological and 40% clinical failure of the current regimen in a community setting (with related poor adherence). These failing patients will probably only be identified through rebound AIDS related symptoms, as viral load testing is unlikely to be available. The same experts predict that at least 20-25% will need a transfer to a completely different regimen in 6-12 months. The following alternative regimens have been suggested as possible 2nd line treatment: zidovudine + didanosine + lopinavir / ritonavir (Kaletra®) zidovudine + didanosine + indinavir
- b) The current d4T-3TC-NVP regimen has to be taken twice daily. However, regimens with efavirenz can be taken once daily, e.g. d4T-3TC-Efavirenz or ddl-3TC-efavirenz. This might improve adherence by patients as it is easier to take. Efavirenz can be

combined with rifampicin containing TB treatment, but is more costly than nevirapine and cannot be taken in pregnancy. Also, a new combination zidovudine + lamuvidine + abacavir (3-in-1 combination tablet; Trizivir®) can be taken once daily, but its price is still 10x more than the current regimen (N36,000/month in private sector).

- c) A scientific review of available products, their cost, and suitability in poor-resource settings should be prepared for the ARV Committee. International HIV experts could be consulted. Negotiations with brand-name and generic drug companies are needed to increase the number of ARVs in the Nigerian market (public and private sector). A meeting with brand name and generic pharmaceutical companies about their anti-retroviral products and prices is indeed over due.

14) **Recommendation XIV: ARV Committee to set up paediatric ART subgroup, and adapt WHO or South African guidelines for Nigeria.**

Initial plans are for 5,000 children to be put on ARV as well, but the current ARV protocol does not (yet) mention a regimen for paediatric AIDS patients. Paediatric AIDS is already a substantial problem in Nigeria. With an average antenatal prevalence of 5.8%, some 350,000 HIV+ pregnancies can be expected in Nigeria annually. Without anti-retroviral treatment or MTCT, these will result in **100,000 babies being born HIV+ every year in Nigeria**. This means a HIV+ baby is born in Nigeria every 5 minutes! The MTCT programme is starting simultaneously with the ARV programme. By coincidence, their six pilot sites overlap with the ARV pilot sites. As the MTCT programme has the ability to avoid 50,000 annual infections, it should obtain equal political support as the ARV Programme.¹¹

15) **Recommendation XV: Ministry of Justice and Commerce to check the status of public health safeguards (parallel import, compulsory licensing, and "Bolar" or early working) in the Nigerian Patents Act.**

UNAIDS-WHO can provide further technical assistance upon request. Nigeria is not classified as a "Least Developed Country," so as a WTO member, its patent legislation had to be TRIPS compliant in 2000. WHO policy recommends that three public health safeguards (parallel import, compulsory licensing, and "Bolar" or early working) are enabled in national legislation.

16) **Recommendation XVI: Government has to approach the ARV producing brand-name and generic producers, and invite them to register their products in Nigeria.**

Drug companies have valid patents in Nigeria¹² for: zidovudine (Retrovir®, GSK), lamuvidine (Epivir®, GSK), zidovudine/lamuvidine combination (Combivir®, GSK), and Saquinavir (Forto-vase®, Roche). The 12 remaining ARVs therefore appear not to be patent protected in Nigeria. They can thus be legally produced by local companies, or imported from generic suppliers. These ARVs include: stavudine, didanosine, efavirenz, indinavir, nelfinavir etc. The importation of generic lamuvidine (3TC) by NASCAP is technically a breach of the GSK patent. However, no response has been noted from GSK. Only two original ARV producing companies (Roche, GlaxoSmithKline) have subsidiaries in Nigeria. Four other original ARV producing companies (Bristol Myers Squibb, Boehringer Ingelheim, Merck Sharpe & Dohme, and Abbott) seem not to be represented in Nigeria. Of the generic ARV manufacturers, Ranbaxy is represented in Nigeria, but Cipla not (yet).

17) **Recommendation XVII: Government to monitor ARV prices closely in Nigeria and internationally call for a meeting with brand name and generic pharmaceutical companies about their anti-retroviral products and prices.**

The current stock of 8000 treatment years of ARVs has been bought early 2001 at a cost of USD 350 (Cipla) and USD 320 (Ranbaxy) per treatment-year. ARV prices have since fallen to even lower levels: the current price is USD 250 pp/year. With an offered discount of 25%, the current price is effectively down to USD 200 pp/year. Private sector prices are far more expensive in Nigeria than in South Africa, where private sector prices have fallen 93% in two years from around USD 10,000 to only USD 700 per treatment-year. In Abuja's private pharmacies,

a month supply of original zidovudine + lamuvidine sells for N 34000, and a month of original nelfinavir for N 52,000. The triple combination therefore costs N 86,000 per month, or over N 1 million per year (= USD 7644 per year). The cheapest triple combination found in Abuja's private sector was a fixed dose combination of zidovudine, lamuvidine and abacavir (Trizivir®, GSK), which sells for N 36000 per month (= USD 3200 per year). This is, however, still 4x as expensive as the cheapest combination in the South African private sector (USD 700 pp/year), and 12x as expensive as the generic cocktail of stavudine, lamuvidine, and nevirapine being used in the ARV Programme (cost to government: N 3000 per month; subsidized cost to patients: N 1000/month). Price reductions are, however, obtainable from the research-based companies: GSK sells zidovudine + lamuvidine through some hospitals in Lagos at a non-profit price of N 11,000 per month.

18) **Recommendation XVIII: Government to launch national and international appeal to sponsor the ARV programme:**

There are clear roll-out plans for the post-clinical trial phase. The original presidential plan mentioned a scaling-up to more sites and ARV patients. Patients will have to buy the ARVs from the revolving drug fund in the health facility, but the State will subsidize the drugs. Although generic ARV prices are likely to drop to below USD 200 pp/year in 2003, alternative ARVs, and salvage therapy will make the treatment more expensive. It is therefore wise to keep planning with a cost of USD 250 pp/year. As the current ARV drugs cost around N 3000/month, Government will have to subsidize drug procurement with N 2000 per treatment-month to reach a consumer price of N 1000/month at health facilities. Assuming 10,000 treatment-years, this amounts to an estimated subsidy of N 240 million in 2002.

Part III

Parameters for a successful long-term ARV programme

The following are parameters that will influence the success of a long-term ARV programme. These are on the one hand ensuring political will/support, information, education, communication, participatory approach, and international partnerships. On the other hand we have standard therapy guidelines, human resources development, financial resources, institutional capacity building, and decentralisation of services. We need further to ensure a continuum of care, cheaper, good quality medicines, diagnostic tests, ensuring strict adherence by patients, down-referral of stabilised patients to near-by health centres, referral for

complications and serious ADRs, collaboration with NGO/CBOs for community home-based care, monitoring and evaluation and operations research.

- 1. Ensure political will/support:** Keep the political leaders well informed about the Programme's progress. Involve all Stakeholders (NASCAP, NACA, States, UN Theme Group, PLWHA, NGOs etc) in advocacy of political leaders. Ensure that leaders at State and Local Authority level are well briefed. Obtain international support (MSF Access Campaign, UN, Global Fund)
- 2. Information, education, communication:** Anything with ARVs will get wide publicity in Nigerian and international press. It would be much better if the press gets info from the ARV programme and not from rumours. Design a communication strategy and a proactive media strategy. Set up a dedicated Information, Education, and Communication (IEC) subcommittee (under ARV Committee). Involve Journalists against AIDS and other communication professionals. Develop informative leaflets about programme (in local languages). Set up a website with information about the ARV programme, and where all technical documents can be downloaded.
- 3. Participatory approach and partnerships:** AIDS is not pure medical problem, and the Health Care System cannot solve it alone. Plan and implement the ARV programme in a participatory approach with PLWHA, NGOs, CBOs, and the non-profit private sector (e.g., CHAN, Islamic Medical Association). International networking can assist the ARV programme with financial and human resources, exchange programmes, training and technical assistance. The ARV Programme should establish good working relations with other public sector ARV Programmes (e.g., Brazil, Uganda, Botswana, Senegal, MSF-South Africa etc), bilateral and multilateral donors; International research organisations, CDC, APIN, Ford Foundation, MRC Banjul etc; professional networks (IAPAC, others); research-based and generic drug companies. (To obtain lower prices for drugs and diagnostics)
- 4. Standard Therapy Guidelines:** Treatment chaos is to be avoided at all costs, in public and private sector. Hence, evidence-based information is the key. NASCAP has to develop standard therapy guidelines and protocols for public and private sector, various health professions (Doctors, pharmacists, nurses, and counsellors), patients (in simple language). As ART science moves rapidly, guidelines and protocols will need to be updated frequently. Guidelines will need to be gently enforced, and practitioners will need to motivate deviation from guidelines to their peers. Deviation from guidelines without valid reasons should be regarded as poor professional conduct, and should be disciplined. For tertiary (referral) level care, where ART is individualised to the patient, knowledge based software systems (such as Therapy Edge) might be appropriate. The software also allows for data capturing and monitoring patients.
- 5. Institutional capacity building:** Existing health care systems are weak, ART is new to Nigeria, and decentralised AIDS structures (SACA, LACA) are still being formed. A strong capacity building programme will be essential for the ARV programme to be rolled out. Government, States, and Local Authorities will need support from UN and development donors. Funding can be found in the HEAP capacity building component (USD 30m available). NASCAP will also need to strengthen its Care & Support unit. For the ARV programme, a dedicated HIV-clinician, pharmacist, and counsellor-trainer will be needed. Finally: there is a tendency in ARV Committee and NASCAP to focus on medical and research capacity. However, it is important to develop also NGO and community organisation's capacity!
- 6. Decentralisation of services:** Clinical trials should preferably be centrally coordinated. However, a roll-out programme to the States and Local Authorities can only be successful if the programme decentralises as much as possible! Communication with the States can be improved through a network of State Coordinators of ARV (SCARVs). In addition, a medical person able/willing to supervise clinical HIV management should be appointed in each of the 6 geo-political zones. This person must be willing to travel, and be acceptable as a clinical supervisor to the health facilities.
- 7. Ensure a continuum of care:** Ensure a horizontal development of ALL services needed for integrated approach: Community Home-based care, Palliative care, Voluntary counselling and (confidential) testing (VCT), Opportunistic Infections, Sexually Transmitted Infections (STIs), Tuberculosis, Mother To Child Transmission

prevention, and not just only ARVs... We need sustainable programmes, not projects! This approach needs teamwork at Federal and State level.

8. **Cheaper, good quality medicines, diagnostic tests:** Competition between research-based and generic industry is key, ensure pricing, and market intelligence at central level, limited tender or direct negotiations. Ensuring efficient procurement, distribution, drug availability: Collaborate with Pharmaceutical Department and WHO's Essential Drug Programme. Define standard operating procedures for: quantification of needs, procurement of drugs and diagnostics, distribution payment, support to Revolving Drug Funds (not only ARVs!)
9. **Human resources, training, supervision, and continuous medical education:** Well-trained and sufficient numbers of human resources are essential for a good national ART programme. Establish a Human Resources Development plan. Establish collaborative agreements with NGOs, PLWHA and AIDS Support organisations for lay counsellors to work in health facilities. Develop links with State-based training centres; develop modular, long-distance education materials for clinicians, nurses, counsellors, and patients. Offer 2-3 day HIV-management courses for clinicians (IAPAC, SA HIV Clin Soc). State Coordinators for ARV (SCARVs) should regularly supervise clinics. Establish Nigerian HIV Clinician Society. Establish a CME programme for HIV management. Consider Therapy Edge for 2nd line referral clinics and private sector
10. **Ensuring strict adherence by patients:** Treatment outcomes of ART depend heavily on strict adherence (95%), which itself depends on: Motivation of patient, Understanding by patient (good counselling), Good patient – doctor relationship, Understanding environment (partner, family, community, AIDS support organisation), Availability and affordability of drugs
11. **Down-referral of stabilised patients to near-by health centres and referral for complications and serious ADRs:** Given the huge numbers, AIDS patients cannot expect to be treated at (tertiary) hospitals. Patients should be properly diagnosed, treated for their acute condition and put on protocolised ARV treatment, and then be down-referred to near-by health centres where dedicated nurses (trained in infectious disease management) can monitor patients on a regular basis. After 6-12 months, 20-25% of the ART patients are expected to need specialised care or secondary treatment due to side-effects, resistance, or therapy failure. Tertiary Hospitals should therefore be reserved for 2nd level AIDS care, and "standard" patients should be treated at State or District hospitals by general doctors.
12. **Collaboration with NGO/CBOs for community home-based care:** The State Health System will be unable to cope with the increasing numbers of terminal, palliative care patients. Collaboration with NGOs/CBOs at State or Local Authority level is needed to ensure proper palliative and home-based care within the community. HBC kits should be made available. Training for community home-based caregivers? Care for terminally ill at home
13. **Financial resources:** An expanded ART programme will consume substantial amounts of financial and human resources. National (NASCAP, HEAP) and international funds (Global Fund) need to be mobilised for programme support. Apply to Global Fund and national development donors. Ensure a national budget for subsidizing ARVs over the next 3 years
14. **Operational research:** Establish a nationwide operational research programme, as many questions are still to be answered: Is a comprehensive ART programme feasible/affordable in Nigeria? Can we use clinical criteria only for ART recruitment? Do we need viral load or can we monitor resistance from clinical failure? Can we use total lymphocyte count to monitor progress (in stead of CD4?) How much survival does ART produce? How can adherence be optimised? Do 3-in-1 combination products improve adherence? Protective efficacy of co-trimoxazol for prophylaxis? Will stigma be reduced by providing comprehensive care? Involve the National AIDS Research Network. Involve international researchers (collaborative approach). Present findings to African and International Conferences (Nigeria is the biggest public sector programme in Africa)
15. **Monitoring and evaluation:** Monitoring should be done by the health workers themselves. The programme can assist by making a minimal dataset of routine data collection. More specific monitoring is best done in a sample of sentinel surveillance centres. An annual national and external evaluation

Section IV

Process oriented early lessons

- It is possible to deliver ARV to PLWHA in public sector facilities.
- Systematic introduction of ARV drugs into the system could actually catalyze the evolution of other health care and support activities for PLWHA, VCCT, laboratories, treatment of OI and home based care.
- PLWHA could take great responsibilities in patient selection, negotiation or prices and especially counselling and home based care.
- That you may not wait for a perfect national health structure to start ART. The basic requirement could be the availability of facilities for evaluating CD4, personnel for counselling, clinicians, and responsible potential for capacity building.
- Public sector/government could possibly initiate and create enabling environment for other establishments to take more direct role in ART provision. Public sector may be more efficient in price reduction, negotiations, monitoring of quality of drugs and practices, technology transfer, local production and assurance of equality and justice with ethnical and legal issues.
- ART administration requires a close regular monitoring of patients as much as of processes. Therefore of appropriate technology for testing, clear guidelines for clinical management as well as well articulated monitoring procedures should be in place.
- Technical, social and financial sustainability is key to a successful ARV Programme

Annex One

AN ACCELERATED CLINICAL TRIAL PHASE IIIB OF A COMBINATION OF STAVUDINE, LAMIVUDINE AND NEVIRAPINE IN THE TREATMENT OF PEOPLE LIVING WITH HIV/AIDS IN NIGERIA

Sponsored by the Ministry Of Health, Abuja July 2001

Edited by Professor E.Essien, Professor C. Wambebe, Professor J. Idoko, Dr O. Idigbe, Dr W. Gashau, Mr I. Saliu, Dr S. Anas-Kolo (Mrs), Professor Jolayemi and Dr Gwarzo.

Introduction

According to UNAIDS¹³, the cumulative figure regarding HIV infection was 37 million people as at the end of December last year. Out of this figure, 25.9 million live in Sub-Saharan Africa (i.e 70%) where only 10% of the world population inhabit. UNAIDS has further indicated that over 80% of new infections of HIV occur in Sub-Saharan Africa. The statistics also show that Africa has suffered a cumulative loss of over 15 million people due to HIV-AIDS complications. In addition to the health statistics, the economic impact due to loss of the productive generation of Africans can only be imagined. The WHO/UNAIDS data further revealed that in some African countries, over 30% of the general population are infected with HIV. Obviously, Africa is bearing the greatest burden due to HIV/AIDS pandemic. Paradoxically, the health facilities in Africa are generally poor; thus further worsening an already very bad situation. In reality HIV/AIDS is more than a health problem affecting the national economy, social life, education, agriculture, industry, etc. It has further been estimated that HIV/AIDS has reversed about 20 years of the regional gains in national development.

According to the National Surveillance study conducted in Nigeria in 1999 by the Federal Ministry of Health¹⁴, about 5.4% of the general population were estimated to be infected with

HIV. Experts have estimated that the current sero-prevalence rate is likely to rise sharply in the years ahead if urgent appropriate interventions are not implemented with total commitment. It is noteworthy that the NACA recently released the HEAP, which is a three year strategy to deal with HIV/AIDS in Nigeria. This response indicates the potential of HIV/AIDS as a real threat to the very existence of our nation. In the last seven years, a commendable response from the Pharmaceutical Industries to the HIV pandemic has witnessed a rapid transformation of the treatment of HIV/AIDS using combination of anti-retroviral agents, especially the Highly Active Antiretroviral Therapy (HAART). In fact, the Delta study¹⁵ shows the clinical superiority of combination therapy using the reverse transcriptase inhibitors (RTIs) over mono-therapy vis-à-vis suppression of viral replication and improvement in the quality of life and prolongation of productive life.

The development of antiretroviral drugs has greatly reduced HIV-related morbidity and mortality in the developed countries. Current guidelines recommend a combination of at least 3 drugs, which should include two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI). This approach has reduced plasma viral loads to undetectable levels in a significant number of patients¹⁶. The objective of the present study is to examine the safety and efficacy of a combination of Stavudine, Lamivudine (both NRTIs) and Nevirapine (an NNRTI). The result of the COMBINE study showed that 2 NRTIs + Nevirapine reduced viral loads to below detectable limits in more patients than 2 NRTIs + Nelfinavir

2. RATIONALE

It is generally acknowledged that there is no cure currently available for HIV/AIDS. However, ARVS have shown that HIV/AIDS can be managed as a chronic disease. For example, treatment with ARVs reduced the viral load to undetectable levels in blood samples, increased the CD4 counts and consequently improved the quality of lives and prolonged the survival of treated patients. In Nigeria and most developing countries, HAART is not feasible due to high cost of the combination therapy, inconvenient dosage schedule and general lack of facilities for appropriate monitoring of the patients. It appears that some serious side effects may be associated with the use of the standard regimen of two NNRTs plus one PI. For example, in a Multicentre Study to Determine the Efficacy and Tolerability of Viracept (Nelfinavir), Zidovudine and HIVID (Zalcitabine) in the Treatment of HIV patients in Nigeria,¹⁷ sponsored by SWIIPHA Nig Ltd involving 26 patients, 14 of the volunteers (i.e. 52%) withdrew from the study due to various reasons including drug related adverse reactions. Recent data¹⁸ suggest that a triple combination of two NRTIs plus one NNRTI manifest comparable (and possibly better) clinical efficacy to the standard regimen of two NRTIs and one PI¹⁹. Such combination has additional advantages of sparing protease inhibitor, convenient dosing schedule, good CNS penetration and exhibited pharmacological barrier to resistance²⁰.

In view of the above, and the urgent need to access ARVs vis-à-vis Nigerian patients,, an Accelerated Phase IIIB Multicentre Clinical Trial will be undertaken to evaluate the safety and efficacy of the triple combination therapy of Stavudine, Lamivudine (NRTIs) and Nevirapine (NNRTI) among Nigerians living with HIV/AIDS. Such triple combination therapy is being used in India with apparently good clinical response (7). The results will indicate whether the good intention of government to use this triple combination therapy among the general population in Nigeria due to their affordability will still be feasible.

b) Specific Objectives:

3) Strategic Objective:

- a) Evaluate the clinical efficacy and safety of a triple combination of Stavudine, Lamivudine and Nevirapine in the treatment of HIV/AIDS.

- i) Determine the clinical efficacy of the combination of Stavudine, Lamivudine and Nevirapine in the treatment of HIV/AIDS.
- ii) Document any side effects related to

- the use of the combination therapy.
- iii) Determine changes in the HIV related symptoms from baseline values.
 - iv) Determine changes in CD4/CD8 ratio and / or absolute CD4 count only.
 - v) Provide clinical, social and psychological support for people living with HIV/AIDS.
 - vi) Determine changes in viral load during therapy with the triple combination therapy.
- 4) **Methodology:**
- a) **Selection of Patients:**
 - i) **Inclusion Criteria:** Male or female (non-pregnant, non-lactating), age > 15 years
 - HIV infection documented by licensed ELISA confirmed by: Western Blot or positive HIV blood culture or positive HIV serum antigen or two Eliza rapid or simple tests based on different principles
 - CD4⁺ cell count > 100/mm³ within 2 weeks prior to entry into the study
 - Ability to provide written informed consent to participate in the trial or explanation in a language he understands very well and thumbing to indicate consent.
 - Ability to comply with the protocol and follow up recommendations after the completion of this study. Anti-retroviral treatment naïve (identified as less than 30 days of any prior antiretroviral therapy)
 - ii) **Exclusion Criteria:**
 - Life threatening opportunistic disease/infection
 - A history of lymphoma
 - Peripheral neuropathy (moderate to severe)
 - Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 4 weeks prior to entry, or an anticipated need for such treatment during the study period
 - Treatment with any immunomodulating agents
 - b) **General Procedures:**
 - i) **Research Team:** The Research Team may include the following experts and professionals: Consultant physician/ haematologist/ paediatrician/ immunologist, pharmacist, pharmacologist, nurse, laboratory technologist, a professional health counsellor and a Trial Manager. The Research Team shall meet before study begins to discuss and agree on the specific modalities, assign responsibilities and draw up an acceptable work plan. All the members of the Research Team will be given an orientation on the project, using predetermined standard procedures.
 - ii) **Patient Population:** Twenty volunteers who satisfy above inclusion criteria will be recruited for the study per center using the following suggested distribution; 2 males and 2 females at WHO clinical stage 1, 3 males and 3 females at WHO clinical stage 2, 3 males and 3 females at WHO clinical stage 3, 2 males and 2 females at WHO clinical stage 4
 - c) **Study Design:** The present study is an open label design.
 - d) **Study Duration:** The study will last for 6-month. However, the volunteers will be followed up for 24 months in the first instance
 - e) **Schedule of Visits for Clinical and Biological Evaluations:** Viral load and CD4 levels shall be assessed at baseline, 3 and 6 months post-drug administration. The volunteers shall visit the clinic for clinical and psychosocial assessment weekly during the first month of therapy. Then fortnightly during the second month and thereafter once a month till the within 4 weeks prior to entry into the study
 - Use of any investigational drug <30 days prior to the start of the study
 - Significant cardiac dysfunction, requiring maintenance therapy with cardiac glycosides, antiarrhythmics or vasodilators
 - Active alcohol or drug abuse to such an extent that, in the investigator's opinion, it will prevent compliance with the dosing schedule and evaluations
 - Severe kidney or and liver dysfunction.

end of the study. Follow up visits shall continue after the study for clinical assessment on a monthly basis for 24 months in the first instance. Samples will be collected from study participants for baseline data a week prior to drug administration then at 3 and 6 months post-drug administration for biological evaluation (see Annex V). Among others, the following evaluations will be performed during visits to the clinic:

- History and physical examination
- Documentation of current medication
- Symptoms related to HIV infection
- Adverse events
- CBC with differential
- LFCs. AST, ALT, bilirubin and alkaline phosphatase. Upon completion of the study, patients will be monitored monthly while laboratory investigations will be conducted on quarterly basis.

- f) **Consent Form:** A consent form is attached as Annex I, which shall be carefully explained to all study participants.
- g) **Ethical Consideration:** All parties will observe strict confidentiality of all the results of this study. The whole study process and procedures will be explained to all study participants and their consent obtained before recruitment. Counselling of patients shall be done at the treatment centres at the beginning and during the course of this study. A consent form will be signed and/or thumb printed by all study participants. The volunteers shall also have the option of withdrawing from the study at any time. ARV treatment to be given free to patients and costs of monitoring throughout the period of investigation and allowances for members of the Research Team will be borne by this project.
- h) **Patient Information Form:** A patient information form is attached as Annex II. It contains relevant information for the volunteers, which should be painstakingly explained to the study participants in a language, which they understand very well.
- i) **Dose Schedule and Administration:** Although these drugs can be taken with, before or after meal, it will be advisable

for each Center to adhere to the use of these drugs immediately after meal.

- i) Patients will be treated with Stavudine 40 mg p.o. 1 capsule bd, Lamivudine 150 mg p.o. 1 tab bd and Nevirapine 200 mg p.o. 1 tab bd.
- ii) During the first 14 days, a dose of Nevirapine 200 mg 1 tab p.o. qd will be utilized to reduce the frequency of rash.
- iii) Patients will continue this therapy for a period of 6 months.

j) **Data Management:** Data will be collected on standard forms, which are subsequently entered into a computer using appropriate software. Prof. Jolayemi of the University of Ilorin is the statistician for this study.

k) **Trial Centres:**

- UNTH, Enugu, Dr. G. Okafor
- UBTH, Benin, Prof. Okonofua
- JUTH, Jos, Prof. J. Idoko
- UMT, Maiduguri, Prof. W. Gashua
- LUTH, Lagos, Dr. C. C. Okanny
- UCH, Ibadan, Dr. Aken'ova
- UITH-Ilorin, Prof. P. O. Olatunji
- Creek Military Hospital, Brig-Gen. S. Njoku
- ABUTH, Zaria, Dr. A. Mukhtar
- UPTH, Port Harcourt, Dr O Ejele
- GSH, Gwagwalada, Abuja, Dr A. Mukhtar
- UDFTH, Sokoto,
- AKTH, Kano, Dr Dutse
- FMC, Uyo, Akwa Ibom
- FMC, Owerri, Imo
- FMC, Gombe, Dr A. Gombe
- FMC, Makurdi, Dr Terna Yawe

5) **RESPONSIBILITIES OF INVESTIGATORS:**

- a) **Principal Investigator (PI):** The PI shall take over-all charge of both laboratory and clinical investigations and participate in follow up activities. He shall also supervise all assessments and ensure their technical quality. The timeliness, accuracy and monitoring of the project shall also constitute parts of the responsibilities of the PI. The PI shall submit the protocol to the Ethics Committees of the participating hospitals for ethical clearance. The PIs for the various centres are indicated in 4.10 above.
- b) **Co-Investigator (CI):** The CI will conduct the preliminary and follow up examinations of recruited volunteers and make appropriate entries as assigned by the PI. The CI may also participate on data management, product quality assurance, blood sample collection, and laboratory investigations.

- c) **Trial Manager (TM):** It is the responsibility of the TM to recruit relevant personnel for the trial and select suitable trial centers. He shall also ensure that the protocol is approved by the NAFDAC prior to the commencement of the study. Furthermore, the TM shall facilitate the availability of all the resources needed for a successful trial prior to the commencement of and during the study. For this study, Dr. S.A. Kolo shall serve as the Trial Manager.
- d) **Monitoring team:** A team of six experts will be responsible for the supervision of the clinical trial centers. At least three supervisory visits should be conducted to each center. The trial manager will head the team.
- 6) **ENDPOINTS OF THE TRIAL: Efficacy Endpoints:** **Primary Endpoints:** development or delay in the development of or resolution of AIDS defining diseases or death and degree of quality of life using Karnofsky performance score. **Secondary Endpoints:** Degree and duration of reduction of HIV load and changes in CD4/CD8 ratio or CD4 from baseline
- 7) **Safety Endpoint:** Development of drug related toxicities sufficiently severe to warrant dose modification; interruption or permanent discontinuation.
- 8) **ADVERSE EVENTS (AE):**
- a) **Definition of an AE:** An AE is an untoward medical occurrence in a study subject administered a pharmaceutical product and which may not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- b) **An AE includes, among others:** exacerbation of a pre-existing illness, increase in frequency or intensity of a pre-existing episode event or condition and continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- c) **Definition of a Serious Adverse Event (SAE):** An SAE is any adverse event that results in any of the following outcomes: Death, a life threatening adverse event, a disability/incapacity
- d) **Clinical Laboratory Abnormalities as AEs:** Abnormal laboratory findings that are judged by the investigator as clinically significant will be recorded as AEs if they meet the definition of an AE. Clinically significant abnormal laboratory findings that are detected after drug administration or that are present at baseline and worsen following the start of the study are included as AEs.
- e) **TREATMENT OF ADVERSE EXPERIENCES:** In case of anaphylaxis and allergic symptoms of dyspnoea or wheezing, itching and erythema, the drugs shall be discontinued. Slow intravenous hydrocortisone 100mg start and slow intravenous promethazine injection 25 mg start should be administered immediately. For mild to moderate skin reactions, oral antihistamine such as chlorpheniramine could be used. Chills and drug fever may be managed using non-steroidal anti-inflammatory agents such as paracetamol and aspirin. Appropriate investigations to rule out other possible causes of fever may be carried out. Abdominal cramps, diarrhoea, nausea and vomiting may be managed with IV fluids, antiemetics, and small feedings with appropriate evaluation of aetiology of diarrhoea. In the event of neurological symptoms, dizziness, and disorientation: the study should be stopped and patient observed in the hospital until the symptoms have resolved completely.
- f) **DOSE REDUCTION/RE-TREATMENT:** If a patient experiences a major toxicity, dosing must be discontinued. Patient should be managed appropriately until symptoms have resolved for several days. For all adverse experiences except anaphylaxis, the drug should be reduced to 50% of offending dose. This may be increased to 75% after a week if tolerated.
- 9) **REASONS FOR DISCONTINUATION OF TREATMENT:** Anaphylaxis or any severe life threatening adverse reactions

NOTES AND REFERENCES

¹ The case study is based on the work of the ARV Committee, "An accelerated clinical trial of a combination of stavudine, lamivudine, and nevirapine in the treatment of

people living with HIV/AIDS in Nigeria" NASCAP Reports and the draft interim report, version 24 February 2002 by consultant Dr Wilbert Bannenberg.

² Confirmatory HIV tests are more expensive, and not widely available. A different rapid or Elisa test is often used for confirmation. In some facilities, "mandatory" testing of inpatients (perceived to be at risk) is done routinely, but without written permission or individually counselling the patients. This practice warrants an ethical discussion. Voluntary counselling and (confidential) testing (VCT) is actively supported by several UN agencies, donors, and NGOs. However, few dedicated counsellors exist in health facilities. The few existing counsellors are mostly nurses and social workers, who already have busy workloads. Doctors are often forced to do the counselling themselves, as dedicated counsellors are not widely available. Hospital budgets are overstretched, and do not allow new staff to be appointed. AIDS NGOs and support groups are active in many States with counselling and awareness work in the community.

³ A pilot programme for the prevention of mother to child transmission (PMTCT) will be launched shortly in six tertiary health facilities (one in each geopolitical zone). Boehringer Ingelheim has agreed to donate the nevirapine. A gradual roll-out is planned to regional hospitals, health centres etc.

⁴ Patients are then given prescriptions, which they struggle to buy in the more expensive private sector. More complicated OI's (e.g. Cytomegalovirus, atypical Mycobacterium, Cryptococcus, non-pulmonary TB) are not easily diagnosed nor treated. Doctors already see many AIDS-patients in hospitals. Two hospitals confirmed that up to 50% of their inpatients were found to be HIV+ in anonymous surveys. A few hospitals have established STI clinics, where PLWHA can get some treatment for opportunistic infections. However, probably due to stigma, no dedicated HIV clinics do yet exist.

⁵ at a cost of up to USD 120 per treatment; this includes cost of tests.

⁶ WHO. (2002) scaling up antiretroviral therapy in resource limited settings: Guidelines for a public health approach.

⁷ A worksheet called "Worksheet on the Action Plan for Accelerated ARVs Access in Nigeria" lists some financial assumptions for the Plan of Action. The cost of 70,000 treatment-years of ARV (10,000 this year, 20,000 in 2003 and 40,000 in 2004) could be around USD 24.5m, assuming the ARV price remains USD 350 pp/year. The actual cost of the cheapest regimen will be less (USD 200-250) but the need for second-line ARVs might increase the cost again. The availability of a dedicated account to purchase ARVs upfront by government will be essential for programme implementation. The planned patient contribution (N 1000/month, or up to N 840m over 3 years) can in theory be credited against this drug budget. For long-term sustainability, lower drug prices or higher patient contributions might be necessary. A future sustainable system will also require efficient revolving drug funds at health facility level. Generic TB treatment costs about USD 35 per cure on the world market. If 33% of the 40,000 patients would need TB drugs, this would cost no more than USD

500,000. However, fewer than 33% would be expected to develop TB, as they are on ARV treatment. The stated USD 14.4m is therefore probably an overestimate. Current cost of a CD4 count is about N 2000 (= USD 15). WHO is investigating cheaper, manual methods? Performing two CD4 counts per year for each ARV patient would cost 70,000 x 2 x USD 15 = USD 2.1m. The government expects the patients to pay for the CD4 counts. The State has agreed to pay for initial laboratory equipment and a basic revolving fund of laboratory reagents and kits. The budgeted USD 28.5m seems a gross overestimate. Viral load can currently only be done at NIMR Lagos, and NIPRD Abuja. Jos University Teaching Hospital and University College Hospital Ibadan might develop this capacity in the near future. The current cost of a Viral Load is N 15,000 -20,000 (=USD 120-150). Performing 6-monthly VL may only be feasible on a small sample of people, as routine VL on all patients would cost up to USD 21m over 3 years. Resistance testing is not yet possible in Nigeria. The nearest facility is probably the CDC lab in Abidjan. Cost of "basic and medical research" (items 2g and 7; total USD 83m !?). Apparently this proposal was based on a "fee" of USD 500 per patient per year. For the clinical trial, the following payments (Naira's) have been budgeted by the clinical trial sponsor. A total of N 13 million has been set aside for the 18 clinical trial sites: this is N 722,000 per clinical trial site, and about N 28,880 per trial subject. Health workers will, however, not be paid in the roll-out phase, and patients are expected to pay for lab tests and consumables via revolving funds

⁸ Generic ARVs have been bought at a cost of USD 350 pp/year from CIPLA (India) and for USD 320 pp/year from Ranbaxy (India). This is a factor 7-10 lower than the existing private sector prices in Nigeria (N 24,000- N 40,000 pp/month; equalling to USD 2133 – 3555 pp/year). The generics are also 50% cheaper than the original products sold at preferential prices to the private sector in South Africa (cheapest triple combination around USD 700 pp/year; see annex 4 for price comparisons). The ARV drugs are stored in Lagos at the National Medical Stores. Initial distribution of the ARVs to the 25 pilot sites was done by courier (UPS). The costs were N 15,000 for a 15-kg pack. No problems were reported during transport. At pilot sites, pharmacists are responsible for the ARV stocks. They are mostly locked up in same cupboards as narcotic drugs. No losses reported so far. 3200 of 8000 the treatment years bought were produced in March 2001, and will expire March 2003. The current 3-months clinical trial of 625 people (25 centres x 25 patients each) will only consume 160 treatment-years of ARVs. Assuming all 625 people can afford to pay for the drugs in the remaining 9 months, only 625 treatment-years will have been consumed by March 2003. This means that at least 2500 new paying patients should be recruited to avoid drug expiry: this is 100 per site. The maximum expansion (given current stocks) is 7375 patients, or 295 per pilot site. A reasonable expansion target could be 250 patients per site. There is no problem finding enough patients: up to 50% of hospital inpatients are HIV+, and most doctors are treating AIDS patients already (O.I.'s only). Three of the four visited pilot sites are already "full" (25 max each as per protocol). The initially selected patients appear to be mainly urban employees, existing chronic AIDS patients and sometimes even hospital staff. Some PLWHA of HIV/AIDS support groups felt excluded as they were not considered for selection. Pressure mounts on

doctors to include more patients, and long waiting lists are already in place.

⁹ Safety monitoring: one serious ADR has been noted: one patient developed general blisters (possible a Stevens Johnson Syndrome?) after 2 weeks, when the NVP dose was increased from 200 to 400mg daily. The patient was admitted, and after the regimen was stopped, the patient improved. Serious adverse events should be reported to the ARV Committee.

¹⁰ The current reporting procedure might be strengthened: maybe the investigators can submit a midterm report after 6 weeks, and provide copies of the patient data so far. The financial arrangements between sponsor (Government) and researchers need further clarification. A budget of N 722,000 per site is available, but no (performance) contracts have (yet) been signed. The payments should ideally be related to trial outputs (correctly monitored patients). It is responsibility of the sponsor (Government) to assess quality of a clinical trial. A monitoring subcommittee has been set up by the ARV Committee for this purpose. Visiting the pilot sites and assessing the quality of care on-site would be an important function. However, if the members are unable to travel extensively in the three months of the clinical trial, they could outsource this task to a small team of "clinical trial monitors."

¹¹ Diagnosis of HIV infection in infants is not easy due to circulating antibodies of the mother, which may give false-positive results with standard HIV tests. HIV-infection in infants may be suspected, if the child of a HIV+ mother is failing to thrive; has recurrent or chronic diarrhoea; has an infection with unusual organisms; has recurrent oral thrush; has recurrent pneumonia; has unexplained anaemia or thrombocytopenia; has generalised lymphadenopathy, hepatosplenomegaly or dermatitis; has severe Herpes simplex stomatitis, zoster or varicella. HIV+ confirmation of a baby/infant before 18 months can only be done by PCR methods. However, PCR is unlikely to be available beyond the research laboratories in Lagos (NIMR) or Abuja (NIPRD). In the absence of a confirmatory PCR test, the status of many babies will remain unclear, and one can therefore speak about "HIV-exposed" babies, where the status is yet undetermined. Diagnosis of seronegativity or sero-reversion (HIV-exposed but not infected) requires any of the two below in the absence of an AIDS-defining illness: two or more negative HIV-antibody tests between six and 18 months of age or one negative antibody test after 18 months, to document the loss of maternal antibodies. Two negative PCRs (with one being done after four months of age). HIV-exposed babies need PCP prophylaxis from 6 weeks (5 mg/kg/day trimethoprim) until proven negative. HIV-exposed babies can receive all standard immunizations, except measles in seriously immunocompromised babies. Confirmed HIV+ infants or HIV-exposed babies with AIDS-related clinical symptoms need more aggressive ARV treatment than adults. This requires specialist care from both paediatricians as parents. Normal CD4 lymphocyte counts are much higher in infancy and decisions about primary prophylaxis and antiretroviral therapy in early childhood should be based on the CD4 percentage. A CD4+

below 15 percent in infants should be viewed in the same light as a CD4 count < 200/ μ l in adults. CD4 counts are useful for monitoring response to antiretrovirals. Viral loads in children are far higher in the first year of life than in adults. They decline to adult values by two to three years of age. At two months of age most infected infants have viral loads above 100 000 copies, ranging from undetectable to 10 million copies/ml. Generally, the higher the viral load, the more rapid the disease progression. ARV Treatment in infants is with anti-retrovirals similar to adults, but requires different dosage forms. Syrups are more expensive, less stable, heavier, and more prone to dosing errors than tablets/capsules. CIPLA India has already offered syrups of zidovudine, lamivudine, and nevirapine to NASCAP, but these products need still to be registered. Nevirapine syrup is available from Boehringer Ingelheim for PMTCT. A detailed protocol should be established for paediatric ARV treatment, once the availability of ARV syrups or paediatric dosage forms has been established.

¹² Amir Attaran (JAMA, 17 October 2001, Vol 286, No 15, page 1888

¹³ UNAIDS: Global HIV/AIDS Report, December 2000

¹⁴ National HIV sentinel survey report: Nigerian Federal Ministry of Health, December, 1999

¹⁵ Delta Coordinating Committee: Delta: a randomized double blind controlled trial comparing combinations of Zidovudine plus didanosine or Zalcitabine with Zidovudine alone in HIV infected individuals. The Lancet 1996; 348: 283 – 292

¹⁶ Saag M, Gersten M, Chang Y et al. Long-term virological and immunological effect of the HIV protease inhibitor (Viracept, Nelfinavir mesylate) in combination with Zidovudine and Lamivudine (abstract).

¹⁷ Multicentre study to determine the efficacy and tolerability of Viracept (Nelfinavir), Zidovudine and HIVID (Zalcitabine) in the treatment of HIV patients in Nigeria. Sponsored by SWIPHA Nig Ltd, 1999.

¹⁸ Ibid.

¹⁹ Bartlett, G. Medical Management of HIV Infection, Johns Hopkins University School of Medicine, 1999.

²⁰ Ibid.