

THE EVOLUTION OF ANTI-RETROVIRAL THERAPY IN NIGERIA

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SUMMARY

This historical review examines developments in anti-retroviral therapy research over the years. International milestones in the treatment of HIV from 1984 to 2011 are described. Using results of a PUBMED literature search, the evolution of HIV therapy in Nigeria is examined. Areas of research highlighted are the Monitoring of ART, adherence to ART, and highly active anti-retroviral therapy in Nigeria. From the first report on the PUBMED search by Akanmu *et al* from Lagos in 2001 to reports in 2013, it is undeniable that HIV scientists in Nigeria have produced a good number of very informative and relevant results in the area of anti-retroviral therapy research in Nigeria.

Key words: Medical History, Anti-retroviral therapy, HAART, Nigeria

INTRODUCTION

HIV/AIDS not only represents the most severe epidemic in modern times, but also the greatest public health challenge in history¹. Nigeria, the most populous country in Africa, has continued to be a reference point of evaluation of progress within the continent. Often referred to as the giant of Africa, there is little doubt that we do have giant challenges, one of which is the scourge of HIV-AIDS. The National Agency for the Control of AIDS (NACA) estimated that as at 2010, 3.1 million Nigerian were living with the virus and that the annual HIV positive birth was 56,681. The agency also estimated that every year about 281,180 new infections occur and, about 1,512,720 people living with HIV required Anti-Retroviral Therapy.

Highly Active Antiretroviral Therapy (HAART) remains the single most significant advance in the field of HIV research. The Clinical Pharmacology of drugs used in the treatment of the virus has undergone rapid evolution over the years. In 1983 the virus was simultaneously identified and isolated by two research teams led by Luc Montagnier and Robert Gallo. Following the isolation of the virus, efforts aimed at developing a diagnostic antibody test yielded positive results. The isolation of the virus and diagnostic test led to the development of methods of screening of agents that could inhibit or eliminated the virus from infected individuals.

The first agent that showed promise in vitro was Zidovudine (AZT) and in 1987 the drug was tried in humans for the first time. The use of the drug resulted in improvement of the survival of HIV infected individuals and, very remarkably, the reduction of

mother to child transmission. However, the drug had significant side effects as a result of which efforts at identifying more anti-retroviral agents were intensified. Not long after, three other Nucleoside Reverse



Luc Montagnier

Transcriptase inhibitors (NRTIs), zalcitabine (ddC), didanosine (ddI) and stavudine (d4T), were tried and approved for use in HIV-1 infection. Within a couple of years the well known groups of anti-retroviral agents were approved for the treatment of HIV-1 in humans (Fig 1).

The next significant milestone in the evolution of ART was the use of drug combinations of agents which proved to be many times more effective than single agents^{3,4}. Although initial trials resulted in an increase in toxicity, combination therapy was found to be more

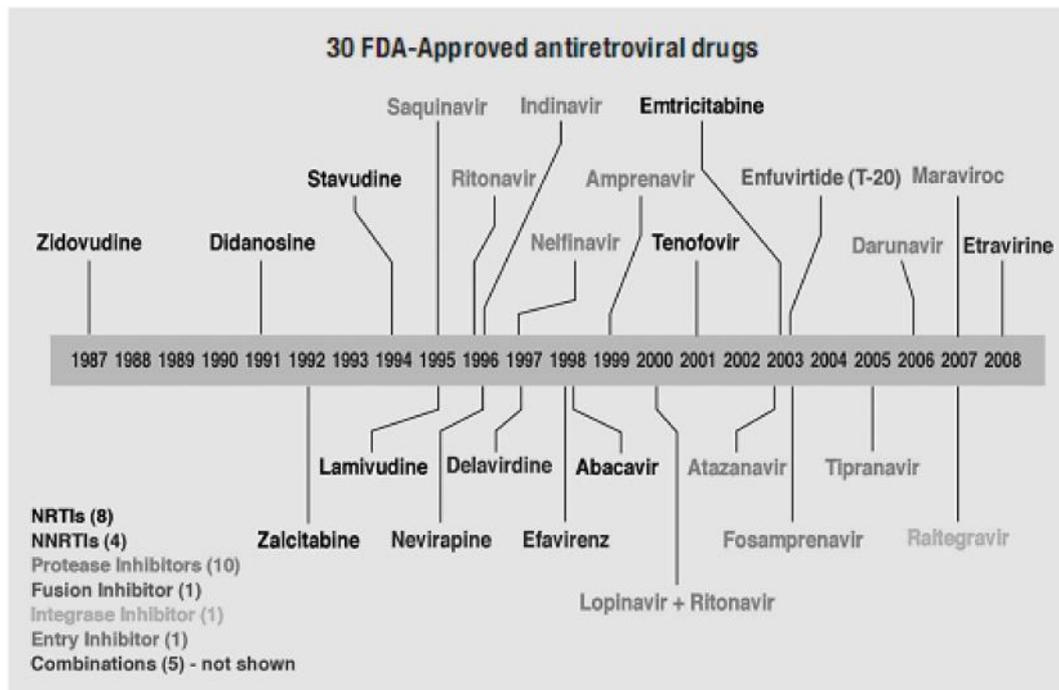


Fig 1: Antiretroviral drugs approved for use in humans².

effective and led to delay in the development of drug resistance. With careful selection, and the use of agents in different anti-retroviral groups, toxicity could be reduced. Very rapidly, highly active anti-retroviral therapies (HAART), which are different combinations of different groups of ART in a triple regimen, were formulated. This development remains the most significant milestone in HIV research. The “decade of HAART” began with the 11th International Conference on AIDS in Vancouver, British Columbia, July 7-16, 1996. Two publications by Hammer and others in 1996 and 1997^{3,4} precipitated other studies that provided undeniable evidence in support of the use of combination therapy in the treatment of HIV-AIDS; the foundation studies that gave birth to the era of HAART.

Today, international and national guidelines and policies of management of HIV are based on HAART. HAART significantly slows down the progress of the virus and diseases in infected humans. The regimen has turned HIV infection from an inevitably fatal condition into a chronic manageable disease, however, in resource limited countries challenges with anti-retroviral therapy include problems with adherence, availability, cost, attitudes towards the disease, monitoring of viral loads, assessment of plasma or other body fluid drug levels, monitoring of CD4 counts, and drug toxicity.

Milestones in the Development of Anti-Retroviral Therapy (ART)

From the discovery and approval of AZT to the present, the treatment of HIV has undergone significant changes. Every milestone has led to improvements in treatment outcome. The development of protease inhibitors, the possibility of reducing mother-child transmission of the virus, discovery of latently infected long-lived HIV cellular reservoirs, preliminary positive results of trials using triple drug combinations, with sustained decrease in plasma HIV viral load, approval of first single-tablet combination of three drugs from two classes (efavirenz, emtricitabine, tenofovir), and Demonstration of the benefits of early initiation of anti-retroviral therapy, with subsequent modification of the international guidelines are very significant milestones (table 1)¹.

ART Research in Nigeria

At this point we shall examine key researches that have documented the progress and evolution of ART in Nigeria. The evolution of ARTs in Nigeria as documented in this historical review was put together after a PUBMED search conducted on 30th November, 2013, using EndNotes™ software version 7.0. The search was done using the terms antiretroviral therapy [title] AND Nigeria [any field]. Retrieved manuscripts were evaluated by the author and relevant abstract were summarized appropriately to fit into the scope of this review. Only a small

proportion of retrieved publications were reviewed in this narrative. Selection of publications reviewed was not based on any particular criteria.

Monitoring of ART

Of the eighty publications retrieved, 53 (66.25%) were on clinical use and monitoring of different ART regimens. The search for alternative to CD4 count as a biomarker of disease progress led to the study by Akanmu and others at Lagos in 2001⁵. The authors compared absolute lymphocyte count (ALC) and complete CD4 T-lymphocyte counts (CCC) as markers of disease progress before and during anti-retroviral therapy. However, they concluded that ALC correlates weakly with CCC in patients undergoing anti-retroviral therapy and it may not serve as a perfect surrogate for CCC as a monitor of immunological response to therapy. This report was the first publication on ART on PUBMED using the search criteria described above. The use of ALC in Nigerians patients would have reduced the cost of investigations in our local population of patients but the study found that ALC was not as reliable as CCC. In 2006, Erhabor and others from Port Harcourt reported findings that showed that Absolute lymphocyte count could become a minimal inexpensive alternative to CD4 lymphocyte count in conjunction with WHO staging and clinical status of patient in determining the optimal time to initiate therapy particularly in resource limited settings where other expensive methods of CD4 enumeration are unavailable⁶. Thus, there is the need to gather more evidence in this area of research to answer the question of whether ALC and CD4 counts could be used interchangeably or to develop models that will make them interchangeable in our resource-limited setting.

Adherence to ART

The effectiveness of any pharmacologic intervention depends on compliance to therapy. Researchers in Nigeria have worked considerably in the area of patient adherence to therapy. Iliasu and others from Kano were first to report that educational status of patients was the key factor that influenced compliance. They found that the better educated the patient is the better the compliance. However, the main reasons they identified for non-adherence to medications were non-availability of drugs, forgetfulness, and lack of funds⁷. In 2008, Olowookere and others in a study done at Ibadan confirmed that there are problems with patient adherence to therapy in a study that showed that non-adherence to HAART is a significant problem in the ARV clinic and that the feeling of being healthy, forgetfulness, and unwillingness to disclose HIV status by people living with HIV AIDS (PLWHA) were significant barriers to adherence⁸. They recommended that efforts towards enhancing patients' adherence

should be made at ART clinics along the lines of the issues discovered. This recommendation is even more relevant today with the scale up of HAART in every region of the country.

Highly Active Anti-Retroviral Therapy (HAART)

As described above, the HAART era started in 1996 following the publication of studies that showed the greatly enhanced efficacies of triple therapies in the management of HIV-AIDS. Ten years later, in 2006, Erhabor and others reported the benefits of HAART on a Nigerian population of people living with HIV-AIDS (PLWHA) from Port Harcourt. Their study showed that HAART significantly improved the immune and clinical status of the subjects studied⁹. Two years later, this finding was also confirmed by Olawumi and others at Ilorin¹⁰. In 2007, Chama from Maiduguri showed that a triple combination of nevirapine, stavudine and lamivudine in pregnancy significantly reduced mother-child transmission of the virus¹¹. Also, in 2007, Idoko and others studied the use of various direct observation therapy of HAART treatment support modalities in Jos, Nigeria¹². The study revealed that treatment outcomes were much better in the treatment-supported groups compared with the control self-therapy group. The paper concludes by strongly recommending the use of treatment support in the Nigerian settings. The most recent paper from the search, however, revealed findings that showed that Nigerian patients are already accumulating mutations associated with resistance to HAART. This information is very relevant to the continued success of the highly drug-dependent measures aimed at controlling the virus in Nigeria.

CONCLUSION

HIV-AIDS is a vibrant area of research in Nigeria. Although research here is highly driven by international ideas and publications, HIV scientists in Nigeria have produced a good number of very informative reports. Only a small proportion of the total number of publications retrieved by the PUBMED search could be reviewed in this historical narrative. The search criteria which were restricted to PUBMED and the publications selected and cited are limitations of this historical review.

In 2001 the African Summit on HIV/AIDS took place at Abuja, Nigeria. The UN General Assembly Special Session on AIDS resolved to scale up a comprehensive response involving prevention, treatment, care and support. At the summit Kofi Annan proposed the creation of a Global Fund to fight AIDS, Tuberculosis, and Malaria. This proposal led to increased funding of efforts at reducing the prevalence of the disease by providing free treatment for those living with the virus.

This has significantly and positively impacted on the epidemiology of the virus in Nigeria. However, HIV scientists in Nigeria need to develop original ideas with more forceful and beneficial local impact. There is also an urgent need to fund the training of our best brains by international collaborations and networks. Infrastructural development is also urgently required to enhance capacity for Basic and Molecular research upon which clinical research should be based and interpreted. Stronger policies towards non-pharmacologic interventions that will further drive down the incidence of the disease should be scaled up. While HIV-AIDS remains a significant challenge in Nigeria, our hope of overcoming this challenge remains the primary responsibility of every Nigerian.

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