

Cost-effectiveness of alternative strategies to start antiretroviral therapy in Nigeria: A model-based analysis

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Abstract

The aim of this paper was to study the cost and health outcomes measured by Disability-Adjusted Life Years (DALYs) and cost-effectiveness of old and new methods with regard to the initiation of antiretroviral therapy in HIV/AIDS patients in Nigeria.

Decision-analytic tree and Markov model were used to evaluate the clinical and economic consequences of the new WHO recommendations. Two arms of initiation evaluated were the deferred therapy arm (CD4<350cells/ml) and the immediate therapy arm (CD4 > 500cells/ml). Major outcome measures were DALYs averted, percentage DALY averted, costs from health payer's perspective, Incremental cost and Incremental Cost-Effectiveness Ratio (ICER). The main input parameters were hazard rates from the Strategic Timing of Antiretroviral Treatment (START) trial and risk of sexual transmission of HIV, disability weights, adjustment rates, discount rates, life expectancy, and the annual cost of treatment, cost of clinical events, death and transmission. Deterministic and probabilistic sensitivity analyses (Monte Carlo simulations) were then executed. The immediate ART arm caused 0.595 DALY averted compared with the delayed arm. This is equivalent to a 94% DALY averted. It also caused a reduced financial burden of -\$345.93. The incremental cost-effectiveness ratio was -\$581.00 (dominant). This ICER was robust to both probabilistic and deterministic sensitivity analyses.

For the Nigerian healthcare system, starting antiretroviral therapy in HIV/AIDS patients with CD4 count > 500cells/ml was found to be less costly and more effective than the old initiation strategies. The decision to adopt the new strategy by the Nigerian health policy makers is highly justified.

Keywords: Cost-effectiveness analysis, antiretroviral therapy, HIV/AIDS, Nigeria.

Introduction

The HIV/AIDS pandemic has significantly influenced the economy, the workforce, individual employees and their families; healthcare costs, labor costs, savings and investments. In developing countries, AIDS is the second leading cause of death among adults [1]. By 2020, HIV is expected to be responsible for approximately 40% of all infectious illness deaths [1]. AIDS, in particular, has a high expensive consequence, especially for the poor. Because AIDS strikes people at their most productive years, it has a negative impact on worker productivity, family income, and national income. The gap between available funding and care demands is widening as the pandemic progresses. The entire cost of care in developed countries has steadily increased owing to an increase in the number of AIDS cases, longer survival times, and increased use of costly therapies [1]. Total HIV/AIDS spending in lower middle-income countries (LMICs) increased from \$4.0 billion in 2000 to \$19.0 billion in 2016. Most of these potential resources are concentrated in 10 middle-income countries, including Nigeria [2].

Antiretroviral therapy (ART) is the main therapy for the management of HIV, although different methods have been involved in its initiation. Initially, the World Health Organization (WHO) recommended the initiation of therapy just for patients at a highest risk of morbidity and mortality, of which most patients in this category had low CD4 cell levels [3]. In recent years, three major randomized controlled trials: START, TEMPRANO and HIV Prevention Trials Network (HPTN 052), demonstrated the clinical benefit of early initiation of antiretroviral therapy [4]. The outcome of these clinical trials led to the WHO's gradual increase in the initiation thresholds. As of 2015, recommendations were made for therapy to be administered instantly to all patients irrespective of CD4 levels [4]. This includes patients with CD4

cell count >500cells/ml.

Nigeria has the second largest HIV epidemic in the world [5], although its prevalence among adults (1.4 %) [5] is much less than in other sub-Saharan African countries such as South Africa (18.9%) and Zambia (12.4%) [6]. Her estimated population as of 2019 was 200 million [7]. This means that considering the prevalence of 1.4%, 2.8 million people were living with HIV in 2019. Unprotected heterosexual sex accounts for 80% of new HIV infections in Nigeria, with the majority of remaining HIV infections occurring in key affected populations such as sex workers [8].

The WHO guideline of 2015 has been adopted for Nigeria as shown by the Nigeria National Strategic plan and implementation, which has commenced at the facility level [9]. This gives a pointer to the increased resources (human, financial, institutional, material) and policy requirements [9]. More so, when the relatively high prevalence of this disease has to be considered, there is great cause for concern as annual per capita health-care expenditures for Nigeria are not as high as those applicable to high-income and upper-middle-income countries. Besides, there has been the problem of donor stagnation since 2015 with the high-income countries decreasing their foreign aid. Domestic funding for the HIV response now exceeds funds provided by international donors, accounting for 57% of the global total funding in 2015. In the face of donor stagnation, there is increasing emphasis on countries most affected by HIV to finance their responses and find more efficient and cost-effective ways to do so [8]. Given the above facts, it will be relevant to ascertain the affordability of the 2015 ART initiation strategy to the National health systems of Nigeria.

This was achieved using the generic DALY framework [10] provided by the global disease burden report. Previous studies reported that the clinical and economic value of the 2015 guideline was on the basis that ART prevents transmission rather than treating infection [4]. As a result of this, the findings from a recent systematic review/meta-analysis assessing the risk of sexual transmission of HIV/AIDS with and without ART treatment was included as part of the input parameters.

Objectives

The aim of this paper was to study the cost, health outcomes measured by DALYs and cost-effectiveness of old and new methods with regard to initiation of antiretroviral therapy in HIV/AIDS patients in Nigeria.

Methodology

The Decision Analytic Model and Markov Model [4] were used to evaluate the clinical, economic consequences and cost-effectiveness of initiation of antiretroviral therapy in a model population of HIV/AIDS Nigerian patients (Figure 1). The Markov model was based on a 5-year Markov state-transition cohort with annual cycle lengths and half-cycle corrections. The economic consequences were from the perspective of the national healthcare payers of Nigeria. The simulated populations were HIV positive

individuals with CD4 cell counts >500cells/ml, which population was categorized into two groups:

a. Immediate arm: defined by immediate initiation in to ART (Pathway A Figure1). This arm of initiation was made to simulate the 2015 WHO recommendations because none of the previous recommendations included administration to patients with >500cells/ml.

b. Deferred therapy arm: Defined by administration of ART only when the CD4 count falls below 350 cells/ml or the patient develops AIDS symptoms. (Pathway B in Figure 1, B1 Received Therapy, B2 No therapy). This arm represents the old criteria for initiation which entails only those with a CD4 cell count of below 350 cells/ml to be initiated in to therapy.

Initiation to therapy is expected to occur at a rate of 14% per year and reach 70% by the fifth year. [14]

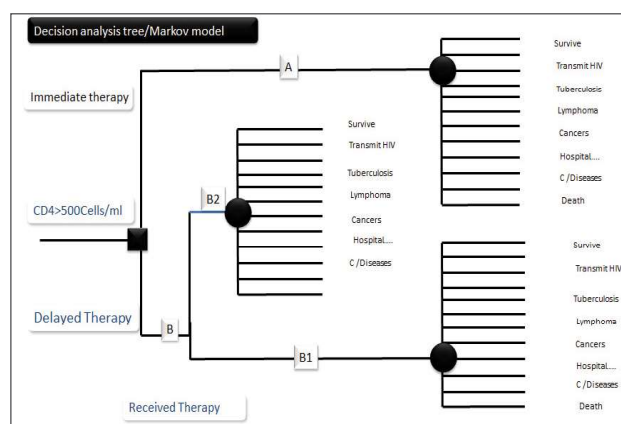


Figure 1. Decision Analytic Tree and Markov model

Outcome measures

The major outcome measures were DALY averted, percentage DALY averted, costs from health payer's perspective, Incremental cost and Incremental cost-effectiveness ratio (ICER).

Disease model

Any patient who enters the model is expected to be followed for 5 years. Each arm of initiation was expected to be controlled or exhibit AIDS-related events such as tuberculosis, Kaposi's sarcoma, malignant lymphoma or NON-AIDS-related events such as cancers, cardiovascular disease or unscheduled hospitalizations. These events were chosen to reflect the occurrence of both AIDS and NON-AIDS-related events that are common to HIV patients across CD4 categories and geographical locations. They could also transmit infections or proceed to death (Figure 1). All events were assumed to be mutually exclusive. The patient in the deferred arm of initiation, in addition to all, could also get initiated to therapy if CD4 cell count reduces to <350cells/ml or they develop AIDS. Model structure and time horizon were carried out in reference to the START trial [4], the strategic timing of antiretroviral therapy (A recent randomized controlled trial with the same randomization of patients to ART therapy).

Model input data

Effectiveness measures

The input data for DALYs computations were hazard rates from the START trial [4] and from a meta-analysis on the risk of sexual transmission of HIV. The disability weights were obtained from the global burden of disease study [11] (Table 1).

Table 1. Model Parameters for Disability-Adjusted Life Years computation

Parameter		
Hazard rates [12]		
Event	Immediate Therapy number/100 person years	Deferred Therapy number/100 person years
Mortality	0.17 (0.08-0.35)	0.30(0.15 -0.61)
Tuberculosis	0.09(0.03 -0.20)	0.28(0.12 -0.75)
Kaposi sarcoma	0.01(0.00 -0.11)	0.16(0.01 -1.00)
Malignant lymphoma	0.04(0.01 -0.15)	0.14 (0.00 -0.30)
Other cancers	0.13(0.06 -0.29)	0.26(0.12 -0.59)
Cardiovascular Disease	0.17(0.08 -0.36)	0.20(0.09 -0.43)
Other hospitalizations	3.94(3.33 -4.64)	4.31(3.65 -5.04)
New transmission	0.85(0.28 -2.99)	5.6 (3.26 -9.62)
Disability weights[12]		
HIV	0.053(0.034-0.079)	Each year for lifetime
Tuberculosis	0.399(0.267-0.547)	6months
Kaposi sarcoma	0.274(0.199-0.411)	3months
Malignant lymphoma	0.274(0.199-0.411)	3months
Other cancers	0.274(0.199-0.411)	3months
Cardiovascular Disease	0.082(0.053-0.117)	2months
Other hospitalizations	0.053(0.033-0.081)	2weeks
New transmission Treated	7.2	7.2, incurred one time at time of infection
Discount rates	0.03(0.00 -0.06)	

These rates were converted to transition probabilities using the natural exponential function. These were converted to prevalence for each event in the two major arms. Prevalence were then computed to DALYs for each arm using standard methodology [11] (Figure 2). All events were assumed to be mutually exclusive. The risk of sexual transmission was obtained from a recent systematic review/meta-analysis [13].

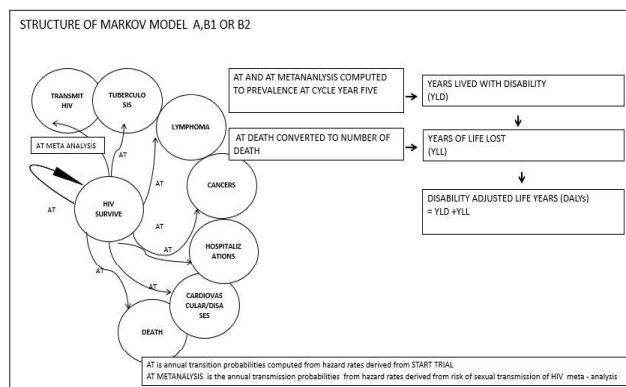


Figure 2. Markov Model and DALY computation

Cost measures

Annual costs for each event were considered. These costs, which were from the perspective of the national healthcare

payers of Nigeria, were ART costs [14] which consist of a sum of the cost of ART, diagnostic tests and personnel costs and PRE-ART costs. All costs were obtained from hospital patients [15]. The cost of ART for year 5 was used to simulate the cost of patients who received ART. This was in addition to the cost of other events, while the cost of PRE-ART simulated the cost of patients who did not receive ART and also included all the event costs. The cost of death, new transmissions (discounted) and cost of each clinical event were included [4] (Table 2). Costs of hospitalization were obtained from relevant published literature adjusted to the present value of 2019 dollars. The GDP per capita was obtained from relevant published sources [16] and life expectancy was of a 25 years old HIV positive patient with CD4 greater than 200 cells/ ml for Nigeria [17]. This life expectancy was chosen to align with 25 years which was the average age for the commencement of ART among HIV patients for Nigeria. The outcome measures were then computed based on standard methodology [11].

Table 2. Model Input Parameters for cost computation

Annual cost inputs (Adjusted to 2019\$)	
Parameter	Cost
ART	\$294.00 [18]
Cost of pre-ART care	\$10.46 [15]
Annual ART drug and management Cost	\$304.46[15]
Cost of tuberculosis	\$122.82 [19]
Cost of Kaposi's sarcoma	\$ 2620.00 [19]
Cost of malignant lymphoma	\$3306 [19]
Cost of other cancers	\$1734 [19]
Cost of Cardiovascular Disease CVD	\$953.38 [20]
Cost of other hospitalizations	\$51.30 [21]
Cost of death	\$63.81 [22]
Cost of new HIV infection, (discounted)	6847. 00 [3]
Average local life expectancy, years	38.20 years [23]
GDP per capita, in 2019 US\$	\$2222.01 [24]

Sensitivity Analysis

Deterministic one-way sensitivity analysis and Monte Carlo simulations

A deterministic one-way sensitivity analysis was carried out by 10%, 20% then 50% increase followed by a decrease in the value of the base-case incremental cost, and then DALY averted to produce a range around the base-case ICER which was reported as tables and tornado diagrams (Figure 3). Probabilistic sensitivity analysis (Monte Carlo simulation) was conducted using 1000 iterations of the base-case incremental cost and DALY averted. The probabilities of the ICERs being dominant and being cost-effective were found.

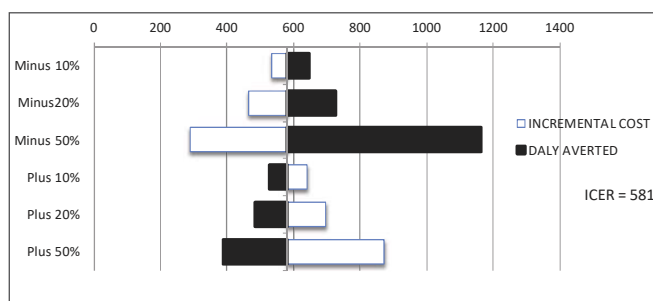


Figure 3. Tornado analysis for Incremental Cost effectiveness ratio for Nigeria.

Statistical analysis

Statistical analysis was done using the Statistical Product and Service Solutions (SPSS) version 22, and STATA software version 12 (STATA Corp., College Station, TX). The STATA software was used in meta-analysis and production of the forest plots.

Results

As shown on Table 3, the immediate therapy arm resulted in a decline in patients cost by \$ 345.93. There is also lower burden of disease in the immediate therapy arm of initiation, which resulted from lower number of clinical events. Dividing the cost by the DALY reduction gave an ICER of -\$581.40 which gives an indication of the immediate therapy arm being dominant when compared to the deferred therapy arm.

Table 3. Cost effectiveness Analysis Base Case Results

Parameters	Immediate ART arm	Delayed ART arm	Base Case Results
Cost per patient(\$)	626.95	972.90	
Incremental cost (\$)			-345.95
Effectiveness (DALYs)	0.035	0.63	
DALY averted			0.595
Percentage DALY averted			94%
Incremental cost effectiveness ratio (Cost per DALY Averted \$)			-581.43
Probability of ICER dominant<0			99%
Probability of ICER<one GDP/Capita			95.6%

Implementation of immediate therapy of initiation accounted for a 94 % reduction of the burden of disease. This shows immense benefit of this recent innovation. The results of the deterministic one - way sensitivity analysis showed the major driver of ICER variation was 50% reduction in DALY averted (Table 4 and Figure 3).

Table 4. Cost effectiveness Sensitivity Analysis Results for Nigeria

Immediate versus deferred therapy	Incremental cost	DALY averted (effectiveness)	Incremental cost effectiveness (ICER) Cost per DALY saved
	-345.95	0.595	-581.43
Decrease in Incremental cost			
A ¹	-311.355	0.595	-523.29
B ²	-276.76	0.595	-465.14
C ³	-172.975	0.595	-290.71
Increase in Incremental cost			
A ¹	-380.53	0.595	-639.55
B ²	-415.13	0.595	-697.70
C ³	-518.9	0.595	-872.10
Decrease in DALY averted			
A ¹	-345.95	0.5355	-646.03
B ²	-345.95	0.476	-726.79
C ³	-345.95	0.298	-1162.86
Increase in DALY averted			
A ¹	-345.95	0.655	-528.57
B ²	-345.95	0.714	-484.52
C ³	-345.95	0.893	-387.62
A -10% B -20% C -50% Changes			

The 1000 iterations in ICER had the probability of the ICER (dominant<0) as 99% and probability of the ICER cost effective (< GDP/capita of Nigeria \$2222.01) as 95.6%. The Meta-analysis for the risk of transmission showed a decrease from 5.6PY (3.26 -9.62) untreated groups to 0.85 PY (0.28 -2.99) treated groups (Figures 4 and 5).

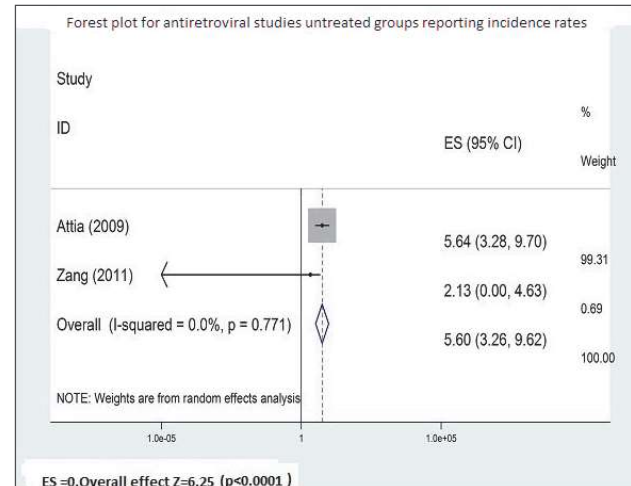


Figure 4. Forest Plot for antiretroviral therapy untreated groups reporting incidence rates.

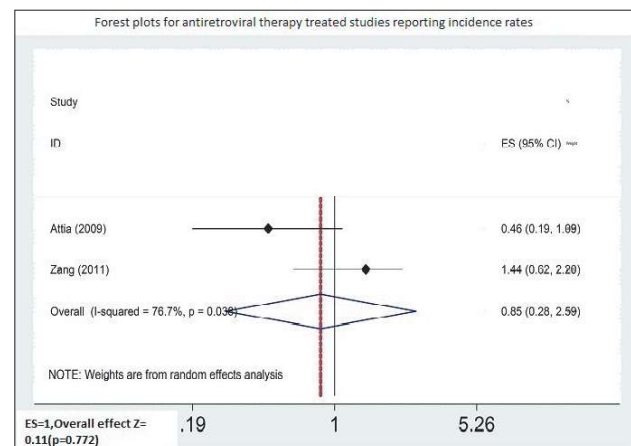


Figure 5. Forest Plot for antiretroviral therapy treated groups reporting incidence rates.

Discussion

The clinical and economic consequences of the new WHO recommendations for starting antiretroviral therapy in Nigeria over five years were evaluated and the findings were as follows: The first major finding was the Meta-analysis that showed 84% reduction in risk of sexual transmission on ART therapy which could translate to positive impact in the community levels as evidenced in a study by Tanser et al [24] although the same authors recommended cluster randomized controlled trials at the population level to verify the findings of the study.

The second major finding is that the new recommendations (methods) dominated the deferred therapy arm by being

more effective and less costly. This is found to be consistent with a recent study that stated that the new recommendations were having more clinical and financial benefits [23]. The Nigeria population of > 200 million people for 2019 [7], the prevalence of HIV/AIDS is 1.4% [5], the highest HIV prevalence age group is 15-49 years [6] and the number of HIV/AIDS patients in this age group is 102,240,177 [6]. The results of this study (DALY averted 0.595/person) may therefore be interpreted to mean a total of 60,832,905 DALYs will be averted for this age group alone and would amount to an increase in productivity of the affected people and for the country.

The negative incremental cost for the new recommendations as implied for this study does not translate to an immediate negative budget impact for the population at the program or the national level but an increase in productivity is most probable. The ICER obtained was most robust to changes in model parameters as Monte Carlo simulations reflecting 1000 iterations of ICERs and showed very high probabilities of ICERs being dominant and being cost-effective.

All findings herein together with the most recent systematic reviews/meta-analyses of the risk of sexual transmission of HIV demonstrate that, for the Nigeria health system, the 2015 WHO recommendations for initiation of antiretroviral therapy are very cost-effective. Such early initiation of ART can enhance the achievement of the Joint United Nations Program on HIV/AIDS (UNAIDS) 90-90-90 targets for ending the HIV epidemic. However, it is noteworthy that these targets cannot be achieved by implementation of this guideline alone. At the population level, success can be more realistically achieved through widespread testing uptake, linkage with care, uptake of therapy, retention of those in therapy, adherence to medications and a favorable social context for the occurrence of all these [18] and reduction of the time between diagnosis and initiation of therapy [23].

Conclusion

For the Nigerian healthcare system, starting antiretroviral therapy in HIV/AIDS patients with CD4 count > 500 cells/ml was found to be less costly and more effective than the old initiation strategies. The decision to adopt the new strategy by the Nigerian health policy makers is highly justified.

Limitations

The model used projected the costs and consequences over five years but could not project for more than 5 years. The model did not put into consideration that the annual transition probabilities and cost for events could vary over the 5 years. Furthermore, in real-world situations, the asymptomatic patients with CD4 counts more than 500 cells/ml may not be motivated to give strict adherence to therapy.

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Conflict of Interest

The authors declare no conflict of interests.

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