Developing Country Studies
ISSN 2224-607X (Paper) ISSN 2225-0565 (Online)
Vol.8, No.1, 2018

Cost Effectiveness of Paediatric Antiretroviral Therapy in Low Resource Settings: The Zambian Case

Bona M Chitah Venkatesh Seshamani*
Department of Economics, University of Zambia

Abstract
This paper presents a cost-effectiveness analysis (CEA) of paediatric ARV administration in Zambia using cotrimoxazole as a comparator. The CEA was facilitated by the paediatric formulations provided by the Indian company Cipla Limited for the CHAPAS (Children with HIV in Africa – Pharmacokinetics and Adherence of Simple Antiretroviral Regimens) randomized controlled trials. The study design for ARVs was an open, randomised and controlled phase I and II trial, in which 220 children were recruited using a set of inclusive and exclusive criteria and randomised on the basis of 1:1 ratio. Two models were used for analysis: Cost-effectiveness analysis and the Markov stochastic model. The integrated results on a number of outcomes such as the CD4 distribution over time, cost estimates, estimates of transition probabilities, estimates of life expectancy, survival curves, incremental cost effectiveness ratios and net health benefits attest the dominance of the ARVs over cotrimoxazole and its high desirability of use as a vital complement to the comparator drug which has its own merit as a low-cost intervention..
Keywords: Paediatric ARV, Incremental Cost Effectiveness Ratio, Markov model, net health benefits, survival analysis

1 Introduction

Life-prolonging antiretroviral (ARV) medication became available soon after the advent of HIV/AIDS. However, the access to these ARVs was severely limited in low-resource settings, especially for children for whom formulations did not exist until the latter half of 2000. To bridge this gap, paediatric formulations were developed.

This paper presents a cost-effectiveness analysis (CEA) of paediatric ARV administration in Zambia using cotrimoxazole as a comparator. The paediatric ARV was Pedimune, a fixed-dose composition of three drugs - Stavudine, Lamivudine and Nevirapine.

The use of CEA for decision making to support choices in the selection of interventions has been weak in Zambia. Such an analysis could therefore provide norms for public choice decisions that improve social welfare in a country like Zambia that is chronically constrained by resources.

The CEA was facilitated by the paediatric formulations provided by the Indian company Cipla Limited for the CHAPAS (Children with HIV in Africa – Pharmacokinetics and Adherence of Simple Antiretroviral Regimens) randomized controlled trials. Such trials provide acceptable international practice standards in patient level data collection and analysis for CEA (Drummond *et al,* 2008).

2 Study design

The study design for ARVs was an open, randomised and controlled phase I and II trial, in which 220 children were recruited from the health facilities based in Lusaka and randomised on the basis of 1:1 ratio. Eligible children were aged 3 months to 14 years inclusive. Treatment of the children in the two treatment arms was based on immediate commencement of ARVs with Pedimune for the first one at full dose. For the other arm the treatment was to be dose escalated over a period of two weeks. In the initial two weeks this therefore entailed a treatment strategy of 50 per cent NVP including additional 3TC/d4T (Lamivir – S) in tabular form. In addition, the children were randomised on the basis of age within the following age categories: 3 months – 6 years and 7 years and above. The children were recruited on the basis of certain inclusion and exclusion criteria as shown below:

2.1 Inclusion criteria

Participation in the study included children with the following characteristics: Children aged between 6 months to 14 years inclusive; children with an HIV-positive status, as determined by positive antibody test in children greater than 18 months or positive proviral DNA in children less than18 months; those previously untreated with antiretrovirals, including any ART given to prevent mother to child transmission, and if they further fulfilled the following conditions:

- They met one of the WHO criteria for initiating treatment which included either of:
- CD4 < 15% if > 18 months of age, or < 20% if < 18 months of age;
- WHO paediatric stage 4 or severe stage 3 disease regardless of CD4 %;
- WHO paediatric stage 2 disease with consideration of CD4 % (<15 for children > 18 months, <20 for children < 18 months).

2.2 Exclusion criteria
The following were excluded:

i. Children who were unwilling or could not regularly attend the CHAPAS trial centre;
ii. Children who faced severe laboratory abnormalities (contraindicated NVP based regimen), i.e. serum creatinine > 5 times upper limit of normal (ULN) or levels of enzymes AST or ALT > 10 times ULN;
iii. Children who had active opportunistic infection and/or serious bacterial infection at the time of study entry including TB (children may be enrolled after the acute phase) and whose life expectancy was less than four weeks;
iv. Children who had current treatment with any medication known to be contra-indicated with any of the drugs prescribed for the patient's ART therapy in this trial, including Rifampicin.

The CHAPAS trial: The CHAPAS trial, as previously mentioned was developed to determine among other issues the efficacy of newly formulated three in one paediatric ARVs. It involved the following procedures:

2.3 ARV administration
ARV administration was monitored on a continuous basis through clinic visits and home visits by both the guardians and clinicians. In addition the following tests were conducted:

- Laboratory tests that included: Haematology (haemoglobin, MCV, platelets, white cell count, neutrophil and lymphocyte counts);
- Biochemistry (Creatine, ALT, AST, bilirubin); Lymphocyte subsets (CD3 – absolute and percentage), CD3 + CD4 (absolute and percentage); CD3 + CD8 (absolute and percentage); Total lymphocyte count;
- Cells and plasma: Virology (HIV – 1 RNA using an ultrasensitive assay)

2.4 Data recording
Data was recorded on case report forms (CRFs). The data collected was recorded in the trial data management system while copies were backed up in the clinical trial clinic.

3 Analytical models

Two models were used for analysis – the Cost Effectiveness Analysis (CEA) model to calculate Incremental Cost Effectiveness Ratios (ICERs) and a Markov model to calculate stochastic net benefits.

3.1 Cost Effectiveness Analysis model
The ICERs were calculated using the following formula:

$$ICER = \frac{C_1 - C_2}{E_1 - E_2}$$

Where
C_1 = *costs related to Treatment Strategy or Intervention* X_1 *(Cotrimoxozole in our case)*
C_2 = *costs related to alternative Treatment Strategy or Intervention X2 (Paediatric ARV)*
E_1 = *the clinical outcomes or effects ascribed to Treatment Strategy* X_1
E_2 = *the clinical outcomes or effects ascribed to Treatment Strategy* X_2

3.2 Net health benefits
The ICER estimates are subject to uncertainty as explained by Stinnet and Mullahy (1998). In order to limit the impacts of problems related to uncertainty and other problems, the concept of Net Health Benefits was developed. The decision making framework is stated as follows:
Assuming,

i. New treatment therapy (or treatment group) and current treatment standard (or control group)
ii. Mean treatment cost of new therapy = μ_{CT} versus that of the control or current therapy = μ_{CC}
iii. Mean effects of new therapy = μ_{ET} versus the control or current therapy = μ_{EC}, then four scenarios arise:

- $\mu_{CT} - \mu_{CC} < 0$; $\mu_{ET} - \mu_{EC} > 0$; dominance - accept the new therapy as it is cheaper and more effective than the current or comparable therapy
- $\mu_{CT} - \mu_{CC} > 0$; $\mu_{ET} - \mu_{EC} < 0$; dominance - reject the new therapy as it is more expensive less effective than the current or comparable therapy
- $\mu_{CT} - \mu_{CC} > 0$; $\mu_{ET} - \mu_{EC} > 0$; trade – off - consider magnitude of additional cost of the new therapy relation to additional the additional cost of the existing therapy.
- $\mu_{CT} - \mu_{CC} < 0$; $\mu_{ET} - \mu_{EC} < 0$; trade – off - consider magnitude of cost-saving of the new therapy relative to its reduced effectiveness

As a summary the following decision making rule or equation holds:

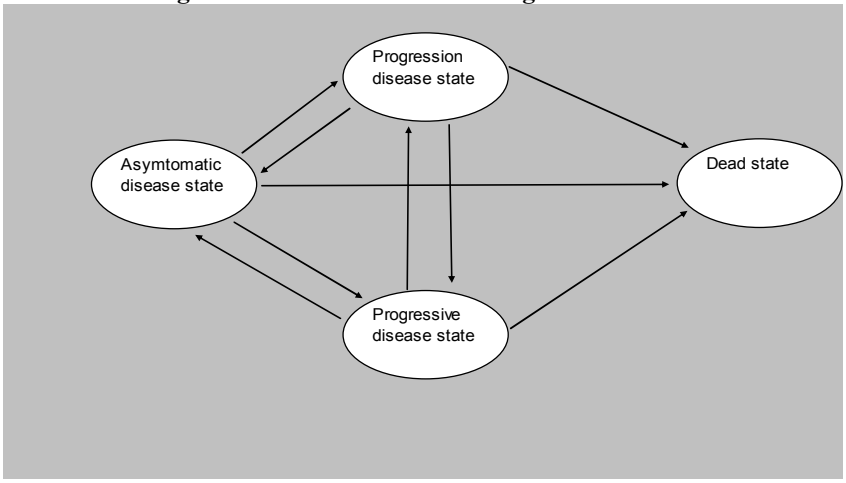
$$\text{ICER} = \frac{\mu_{CT} - \mu_{CC}}{\mu_{CT} - \mu_{CC}} = \frac{\mu_{\Delta CT}}{\mu_{\Delta E}} < R_C$$

3.3 Markov model – key concepts

3.3.1 *Absorbing states:* The Markov model has defined states of health in which the disease progresses. Disease progression is not necessarily irreversible nor is it definite in the sense that within a particular health state, an individual need not necessarily progress to a worse state. Each Markov model will have an *absorbing* state. This is the state from which the individual will not ordinarily experience remission or reversal and is normally called the *dead* state.

The following diagram shows the different states of disease.

Figure 1: Markov Model showing disease states



Source: Sculpher *et al* (2000)

3.3.2 *Transition Probabilities:* Progression through a given state is indicated by the arrows. In the representation above the transition matrix is given by 4 x 4 dimensions meaning that 16 possible transitions exist.

While the individual transits through various disease progression states, the probability of moving out of a given state is not dependant on previous states the person may have encountered.

3.4 Survival analysis

Survival analysis (or time to event analysis, transition or duration analysis) seeks to determine the time between transition and time in state. The outcome of interest in the clinical trials was death. Survival analysis was undertaken to determine the clinical outcome. The end of death was used to determine a number of things which included among others, the resource use up to the time of death, the number of persons living, survival rates, transition probabilities and life expectancy.

The survival analysis using the Kaplan – Meier analysis proceeds by assuming replacement. If survival time is defined as t_1, the cohort or sample size is n_1 and the censoring event affects d_1, *as a share of the sample,* the Kaplan – Meier estimator, $S(t_1)$ is determined by the following:

In time or period t_1 the number of patients who died over the total sample is equal to the probability of surviving = $n_1 - d_1$, *or alternatively:*

$$\text{Probability of surving , Pr} = \frac{n_1 - d_1}{n_1}$$

This process is iterative until censoring ends or the cohort is eliminated. This typically may not happen in a clinical trial due to the budget limitation or time to ensure follow up of the natural course of time to natural event for all subjects.

With each censoring event (death) the Kaplan – Meier curve drops, with the (vertical) distance or drop reflecting the number of censored events. The probabilities of dying in the two arms under consideration are by observation of the curves shown to be much higher for the cotrimoxazole arm in comparison to the ARV arm where the vertical drops are smoother than the former.

3.5 Costing

Costing was done of the following items:

- Costing of the main items such as medications was based on resource use or consumption and valued at market prices using the WHO Drug Price List.
- Human resource costs were estimated using proportion of time spent by patients and the number of

contact time per patient valued by the share of total wage and salary costs by the different skills.

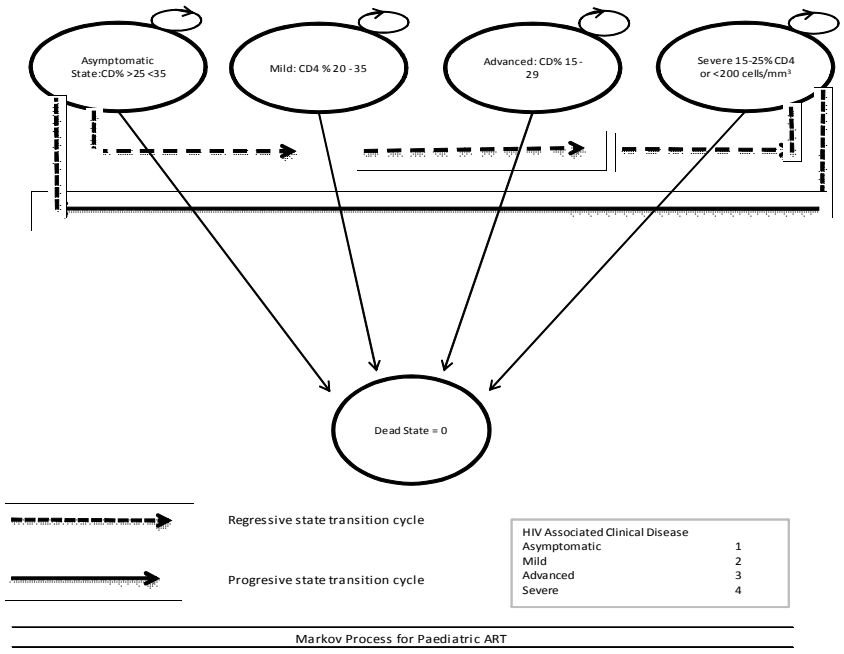
- The building costs are estimated as the share of space occupied and number of paediatric cases with HIV/AIDS as a share of the total paediatric attendance.
- Costs of opportunistic infections were calculated on the basis of hospitalisation costs and costs of opportunistic infection medications.

3.6 Markov chain modelling

Living with HIV/AIDS in all likelihood provides a risk of a long term process that relates to HIV/AIDS being considered a chronic condition. The cohort under consideration in this case had already been infected. Consequently, the typical representation of Markov chain process may be depicted in three generic states of *well*, *ill* and *death*. In this case, the identified states comprise HIV infection in asymptomatic state as well as the two depicting ill health and death. Although some of the subjects in the study may well have initially transitioned from well state to ill, most subjects were already infected by way of mother to child transmission.

In the Markov model depicted in Figure 2 showing the patient cycle, the transition probabilities are estimated based on the Kaplan – Meier method. The circles show a specific health condition or health state. In this case, the health states can be defined in terms of the differences in the CD4 count and/or percentage. Given the complexities of appropriately distinguishing the status of children under 5 in terms of their CD4 counts, a preference for CD4 percentage i.e. CD4 lymphocyte cells as a percentage of total lymphocytes has been advocated (WHO, 2006, Dunn *et al*, 2008). The arrows demonstrate the progression related with transition between or among the different states or disease conditions. In addition, all the different disease conditions obtain under the two different treatment arms of the cohort. The patient life cycle is estimated using Monte Carlo simulation.

Figure 2: State – Transition Markov model



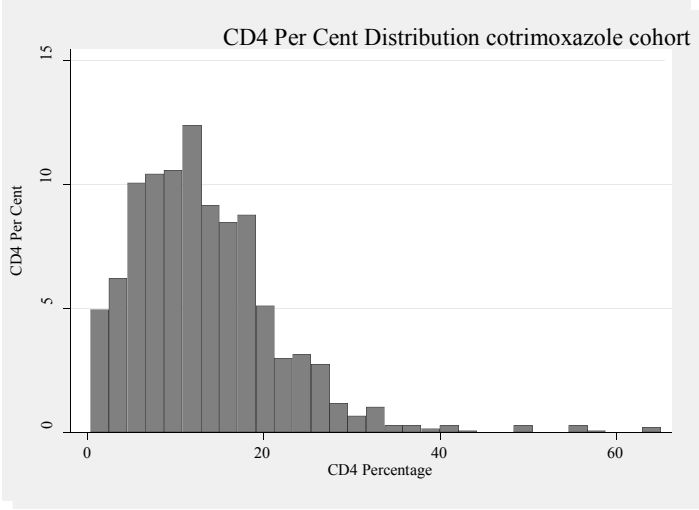
4 Results and their interpretation

We now present the various results emerging from our analysis and their interpretation.

4.1 CD4 percentage distribution over time

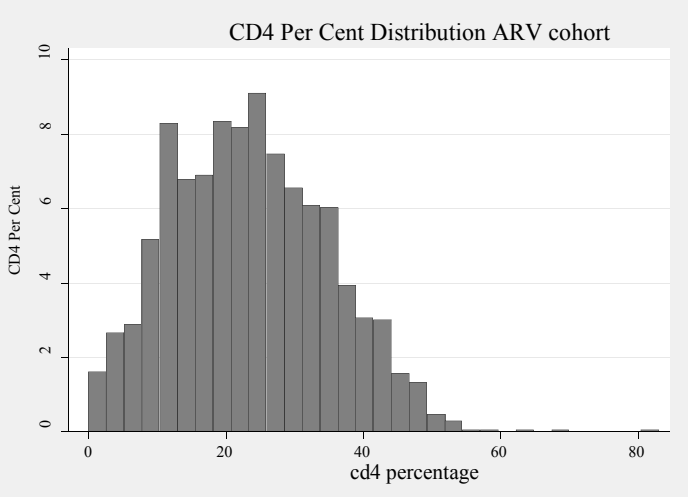
The following histograms show the distributions of the CD4 percentage of the cohorts from initiation of the clinical trials to the end. The data shows the skewness of the CD4 cells over time and the concentration in CD4 as medication was available consistently for the cotrimoxazole and ARV cohorts. Over the duration of the trial, given all the quarterly readings for CD4 percentage and other data, the cohort distribution for cotrimoxazole shows a leftward skewed beta distribution. The ARV cohort on the other hand is right skewed.

Figure 3: CD4 Percentage Distribution of the Cotrimoxazole Cohort



Source: Authors' construction

Figure 4: CD4 Percentage Distribution of the ARV Cohort



Source: Authors' construction

4.2 Cost structures

Table 1: Cost Estimates for Cotrimoxazole Cohort

Variable	Mean		Standard deviation	Minimum	Maximum
Total inpatient cost (hospitalization costs)	250		446.45	0	3859
Total medical costs	45.6		132.8	0	2092
Physician and nursing costs	21.7		7.9	1	115
Laboratory costs	15		0	15	15
Total costs per person	752		551.8	1	4252

Source: Authors' computations

Table 2: Cost Estimates for Antiretroviral Cohort

Variable	Mean costs (US$)	Standard deviation	Minimum	Maximum
Physician costs	65.7	21.8	6	107
Nursing costs	14.7	4.4	1	23
ART costs (including other drugs for outpatient prescriptions)	90.4	70.9	0	307
Total inpatient cost (hospitalisation) costs inclding drugs)	13.4	32.6	0	516
Laboratory costs	15.0	0.0	15	15
Total costs per person	201.5	95.2	24	791

Source: Authors' computations

The structure of the costs for the two treatment arms shows quite diverse results. The costs for ARV are on the whole comparatively low. In particular, the hospitalisation costs are markedly lower than the corresponding costs for cotrimoxazole. The higher hospitalisation costs in the case of cotrimoxizole also reflect the frequency of hospitalisations and the higher costs related to the incidence of opportunistic infections. The cost structures ultimately have a key bearing on the final effectiveness results.

4.3 Transition probability estimates

The transition probabilities were obtained using the approach by Chancellor et *al* (1997). The progression of the disease over time is shown in a four dimensional Markov model. This captures the staging phases of HIV in terms of the states relating to asymptomatic, symptomatic (severe and AIDS) and death.

Table 3 below provides the transition probabilities.

Table 3: Transition probabilities

TRANSITION PROBABILITIES			
Parameter		**Value**	**Value**
Treatment Arm	**Summary of Transition Formulation**	**1.Cotrimoxazole**	**2.Antiretroviral therapy**
Transition probability to A to A	TP_A_A	0.72	0.9
Transition probability to A to B	TP_A_B	0.18	0.08
Transition probability to A to C	TP_A_C	0.098	0.0019
Transition probability to A to D	TP_A_D	0.002	0.001
Transition probability to B to A	TP_B_A	0	
Transition probability to B to B	TP_B_B	0.64	0.748
Transition probability to B to C	TP_B_C	0.34	0.238
Transition probability to B to D	TP_B_D	0.02	0.014
Transition probability to C to A	TP_C_A	0	
Transition probability to C to B	TP_C_B	0	
Transition probability to C to C	TP_C_C	0.6	0.72
Transition probability to C to D	TP_C_D	0.4	0.28
Transition probability to D to D	TP_D_D	1	1

Source: Authors'computations

Note: The transition of an individual, say Individual Y from one state of being to another, reflects in the modelling process the risk of Individual Y changing her/his status based on changes to the CD4 count and therefore her/his ability to survive within the current state, on the basis of the assumptions of the Markovian states. TP = Transition Probability

In general the comparative probabilities for the cotrimoxazole group are lower than for the ARV group.

4.4 Estimates of life expectancy and survival curves

Life expectancy was estimated based on the approach of the declining exponential approximation of life expectancy (DEALE). This assumes that survival rate is dependent on a simple exponential function (Beck JR *et al,* 1983).

Table 4 below shows the estimates of life expectancy for the cotrimoxozole and ARV cohorts.

Table 4: Life expectancy estimates

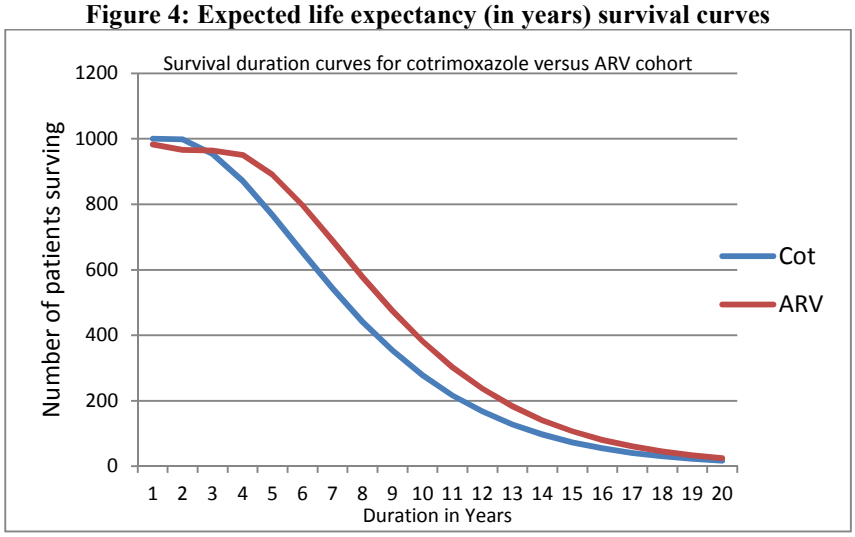
Years in state	A	B	C	Life expectancy (Additional years)
Cotrimoxazole	3.6	1.8	2.4	7.7
ARVs	4.8	1.9	2.3	8.9

Source: Authors' computations

The better performance on life expectancy of the ARVs is clearly brought out in the above table.

The expected life expectancy survival curves are shown in Figure 4 below. The derived survival curves are based on an assumed sample of 1000 iterations (obtained through bootstrapping) and a 20-year period.

Figure 4: Expected life expectancy (in years) survival curves



Source: Authors' construction

Again, the survival rates shown by the curves in the figure above demonstrate the clear capacity of the ARVs to extend life expectancy and shift the curves outwards as a result of increased life expectancy.

4.5 Computed incremental cost effectiveness ratios (ICERs)

Table 5 shows the ICERs for the two treatments.

Table 5: Computed Incremental Cost Effectiveness Ratios

	Cotrimoxazole	ARVs
Expected cost	$3,735	$3,356
Life-years	6.51	7.53
Incremental cost		-379.06
Incremental outcome		1.0166
ICER		-$373

Source: Authors' construction

Theoretically negative ICERs are considered problematic to interpret according to Briggs and Gray (1999) and Stinnett and Mullahy (1998). However, as shown by Stinnett and Mullahy as well as Briggs and Gray, if the ICER is identified to be in quadrant II of the cost–effectiveness plane, then the new therapy or technology is clearly dominant and the complications do not arise. The interpretation is more definitive as the change in the ICER denotes the cost alleviated or saved as a result of the new technology.

4.6 Net benefit estimates

The net benefits as shown in Table 6 below are positive in all cases fulfilling the conditionality and confirming the greater gains accruing by administration of ARVs in relation to cotrimoxazole. When the range of threshold values (lambda) is changed, it is observed that the net benefits are even greater for higher thresholds.

Table 6: Net benefit estimates

Descriptive statistics for Net Benefit	*Net Benefit (US$) Given Λ = US$1,500*	*Net Benefit (US$) Given Λ = US$5,000*
Mean	*21,310*	*69,729*
Median	*21,309*	*69,729*
2.5th percentile	*21,131*	*69,277*
97.5th percentile	*21,506*	*70,147*
Minimum	*20,990*	*69,010*
Maximum	*21,633*	*70,463*

Source: Authors' construction

5 Conclusion

The results of our analysis show that the ICERs favour paediatric ARVs in comparison to the cotrimoxazole. The policy recommendation that emerges from this is that paediatric ARVs constitute a necessary intervention in the care and management of children living with HIV/AIDS in the same way as adults have access to adult formulations.

These results in fact corroborate the results of another recent study by Chitah, Jonsson and Seshamani (2016) on the Health Related Quality of Life (HRQoL) that shows that the administration of paediatric ARVs brings about a very big improvement in the HRQoL of children.

Further, though the results are in favour of ARVs, the results of cotrimoxazole as earlier reported by Mairin R *et al* (2008) show that cotrimoxazole is itself cost effective given the option of doing nothing as was the case at the time or using it to lower infections of opportunistic illnesses as well as delayed advent of AIDS and immunity decline.

All these combined results demonstrate the economic and social gain of adopting and providing public health management of HIV/AIDS using both cotrimoxazole as a low cost intervention and ARVs to sustain the life expectancy of the individual beyond what hopelessness previously existed.

REFERENCES

Beck JR, Pauker, SG (1983), The Markov process in medical prognosis, *Medical Decision Making* 3(4), 419-458.

Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M (1997), Modelling the cost – effectiveness of Lamivudine/Zidovudine combination therapy in HIV infection, *Journal of Pharmacoeconomics* 12(1), 54-62.

Chitah, MB, Jonsson, D, Seshamani, V (2016), Investigating the Health Related Quality of Life of Zambian children living with HIV/AIDS on antiretroviral therapy, *Health Economics and Outcome Research: Open Access* 2(3), 1-5.

Briggs AH, Gray AM (1999), Handling Uncertainty when Performing Economic Evaluation, *Health Technology Assessment* 3(2).

Drummond MF, Schwartz, JS, Jonsson, B, Luce, BR, Neumann, PJ, Siebert, W, Sullivan, SD (2008), Key principles for the improved conduct of health technology assessments for resource allocation decisions, *International Journal of Technology Assessments in Health Care* 24(3), 244 – 258.

Dunn D, Woodburn P, Duong T, Peto J, Philips A, Gibb D, Porter K. (2008), Current CD4 Cell Count and the short – term risk of AIDS and death before the availability of effective Antiretroviral Therapy in HIV – infected children and adults, *Journal of Infectious Diseases* 197(3), 398-404.

Kaplan, E.L., Meier, P. (1958), Non-parametric estimation from incomplete observations, *Journal of the American Statistical Association* 53 (282), 457- 481.

Mairin R, Griffin S, Chitah B, Walker AS, Mulenga V, Kalolo D, Hawkins N, Mary C, Barry MG, Chintu C, Sculphur MJ, Gibb DM (2008), The cost – effectiveness of cotrimoxazole prophylaxis in HIV–infected children in Zambia, *AIDS Journal*, 22, 749 – 757.

Sculphur M, E. Fenwick, K Claxton (2000). Assessing Quality in Decision Analytic Cost–Effectiveness Models, *Phamarcoeconomics,* 17(5) 461 – 477.

Stinnett AA, Mullahy J (1998), Net health benefits: A new framework for the analysis of uncertainty in cost–effectiveness analysis, *Journal of Medical Decision Making,* 18 Supplement: S68 – S80.

World Health Organisation (2006), Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations of a public health approach, Geneva. Switzerland.