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

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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.

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 than 18 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:

\[ \text{ICER} = \frac{C_1 - C_2}{E_1 - E_2} \]

Where

- \( C_1 \) = costs related to Treatment Strategy or Intervention \( X_1 \) (Cotrimoxazole in our case)
- \( C_2 \) = costs related to alternative Treatment Strategy or Intervention \( X_2 \) (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 = \( \mu_{CT} \) versus that of the control or current therapy = \( \mu_{CC} \)
iii. Mean effects of new therapy = \( \mu_{ET} \) versus the control or current therapy = \( \mu_{EC} \), 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:

\[
\text{ICER} = \frac{\mu_{CT} - \mu_{EC}}{\mu_{CT} - \mu_{EC}} = \frac{\mu_{CT}}{\mu_{EC}} < R_C
\]

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**

![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 \(t_i\), the cohort or sample size is \(n_i\) and the censoring event affects \(d_i\), as a share of the sample, the Kaplan – Meier estimator, \(S(t_i)\) is determined by the following:

In time or period \(t_i\) the number of patients who died over the total sample is equal to the probability of surviving = \(n_i - d_i\), or alternatively:

Probability of surviving, \(Pr = \frac{n_i - d_i}{n_i}\)

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.

![Markov Process for Paediatric ART](image_url)

**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.
4.2 Cost structures

Table 1: Cost Estimates for Cotrimoxazole Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total inpatient cost (hospitalization costs)</td>
<td>250</td>
<td>446.45</td>
<td>0</td>
<td>3859</td>
</tr>
<tr>
<td>Total medical costs</td>
<td>45.6</td>
<td>132.8</td>
<td>0</td>
<td>2092</td>
</tr>
<tr>
<td>Physician and nursing costs</td>
<td>21.7</td>
<td>7.9</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td>Laboratory costs</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Total costs per person</td>
<td>752</td>
<td>551.8</td>
<td>1</td>
<td>4252</td>
</tr>
</tbody>
</table>

Source: Authors’ computations
Table 2: Cost Estimates for Antiretroviral Cohort

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

*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 cotrimoxazole 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

<table>
<thead>
<tr>
<th>TRANSITION PROBABILITIES</th>
<th>Parameter</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to A to A</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to A to B</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to A to C</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to A to D</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to B to A</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to B to B</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to B to C</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to B to D</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to C to A</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to C to B</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to C to C</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to C to D</td>
<td>TP_a</td>
</tr>
<tr>
<td></td>
<td>Summary of Formulation</td>
<td>Transition to D to D</td>
<td>TP_a</td>
</tr>
</tbody>
</table>

*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 cotrimoxazole and ARV cohorts.
Table 4: Life expectancy estimates

<table>
<thead>
<tr>
<th>Years in state</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Life expectancy (Additional years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
<td>3.6</td>
<td>1.8</td>
<td>2.4</td>
<td>7.7</td>
</tr>
<tr>
<td>ARVs</td>
<td>4.8</td>
<td>1.9</td>
<td>2.3</td>
<td>8.9</td>
</tr>
</tbody>
</table>

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

4.5 Computed incremental cost effectiveness ratios (ICERs)

Table 5 shows the ICERs for the two treatments.

Table 5: Computed Incremental Cost Effectiveness Ratios

<table>
<thead>
<tr>
<th></th>
<th>Cotrimoxazole</th>
<th>ARVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected cost</td>
<td>$3,735</td>
<td>$3,356</td>
</tr>
<tr>
<td>Life-years</td>
<td>6.51</td>
<td>7.53</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>-379.06</td>
<td></td>
</tr>
<tr>
<td>Incremental outcome</td>
<td>1.0166</td>
<td></td>
</tr>
<tr>
<td>ICER</td>
<td>-$373</td>
<td></td>
</tr>
</tbody>
</table>

Source: Authors’ construction

Theoretically negative ICERs are considered problematic to interpret according to Briggs and Gray (1999) and Stinnett and Mullaly (1998). However, as shown by Stinnett and Mullaly 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

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

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