APPLICATION OF ECONOMIC ANALYSIS TO EVALUATE VARIOUS INFECTIOUS DISEASES IN VIETNAM

by

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ABSTRACT

This thesis is composed of two economic evaluations: one trial-based study and one model-based study. In a recent study published in *Clinical Infectious Diseases* in 2011, a team of OUCRU investigators found that immediate antiretroviral therapy (ART) was not associated with improved 9-month survival in HIV-associated TBM patients (HR, 1.12; 95% CI, .81 to–1.55; P = .50). An economic evaluation of this clinical trial was conducted to examine the cost-effectiveness of immediate ART (initiate ART within 1 week of study entry) versus deferred ART (initiate ART after 2 months of TB treatment) in HIV-associated TBM patients. Over 9 months, immediate ART was not different from deferred ART in terms of costs and QALYs gained. Late initiation of ART during TB and HIV treatment for HIV-positive TBM patients proved to be the most cost-effective strategy.

Increasing resistance of *Plasmodium falciparum* malaria to *artemisinin* is posing a major threat to the global effort to eliminate malaria. *Artesmisinin* combination therapies (ACT) are currently known as the most efficacious first-line therapies to treat uncomplicated malaria. However, resistance to both *artemisinin* and partner drugs is developing and this could result in increasing morbidity, mortality, and economic costs. One strategy advocated for delaying the development of resistance to the ACTs is the wide-scale deployment of multiple first-line therapies. A previous modeling study examined that the use of multiple first-line therapies (MFT) reduced the long-term treatment failures compared with strategies in which a single first-line ACT was recommended. Motivated by observed results of the published modelling study in the Lancet, the cost-effectiveness of the MFT versus the single first-line therapies was assessed in settings of different transmission intensities, treatment coverages and fitness cost of resistance using a previously developed model of the dynamics of malaria and a literature –based cost estimate of changing antimalarial drug policy at national level. This study demonstrates that the MFT strategies outperform the single first-line strategies in terms of costs and benefits across the wide range of epidemiological and economic scenarios considered. The second analysis of the thesis is not only internationally relevant but also with a focus towards healthcare practice in Vietnam.

These two studies add significant new cost-effectiveness evidence in Vietnam. This thesis presents the first trial-based economic evaluation in Vietnam considers patient-health outcome measures as the participants have cognitive limitations (tuberculous meningitis), dealing with missing data along with the potential ways to handle this common problem by the use of multiple imputation, and the issues of censored costs data. Having identified these issues would support the decision makers or stakeholders including the pharmaceutical industry to devise a new guideline on how to implement a well-design trial-based economic evaluation in Vietnam in the future. Another novelty of this thesis is the introduction of the detailed of costing of drug regimens change in which the economic evaluations considering the drug policy change often do not include. This cost could be substantial to the healthcare system for retraining the staff and publishing the new guidelines. This thesis will document the costs incurred by the Vietnamese government by changing the first-line treatment of malaria, from single first-line therapy (ACT) to multiple first-line therapies.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ACT	Artemisinin-based combination therapy
ACTG	AIDS clinical trials group
AEs	Adverse events
AIDS	Acquired immune deficiency syndrome
AL	Arthemether-lumefantrine
ART	Antiretroviral therapy
ARV	Antiretroviral drugs
ASAQ	Artesunate-amodiaquine
AZT	Zidovudine
c.i.f	Freight and insurance costs
CAMELIA	Cambodian Early Versus Late introduction of antiretroviral
CBA	Cost-benefit analysis
CC	Complete cases analysis
CD4 count	A lab test that measures the number of CD4 T lymphocytes (CD4) in a sample of your blood
CEA	Cost-effectiveness analysis
CEAC	The Cost-effectiveness acceptability curves
CHEERs	Consolidated heath economics evaluation reporting standards
CI	Confidence interval

CNS	Central nervous system
CPI	Consumer price index
CQ	Chloroquine
CR	Fitness cost of resistance
CSF	Cerebrospinal fluid
CUA	Cost-utility analysis
CV	Contingent valuation
CV8	Dihydroartemisinin, piperaquine, trimethoprim and primaquine
DALYs	Disability adjusted life years
DHA-PPQ	Dihydroartemisinin- piperaquine
DOTS	The directly observed treatment, a short-course
EC study	Economic evaluation of timing of ART to treat HIV-associated tuberculous meningitis patients
EFV	Efavirenz
EE	Economic evaluation
EIR	Entomological inoculation rate
EPTB	Extra-pulmonary TB
EQ-5D	A standardized instrument for use a measure of heath outcome
EVPI	Expected value of perfect information
GCS	Glasgow coma scores
GDP	Gross domestic product

GF	Global fund
GIS	Geography information system
GML	A generalized linear model
GNI	Gross national income
HCV	Hepatitis C
HIV	Human immune deficiency virus
HIV-1RNA	Plasma HIV-1viral load
HR	Hazard ratio
HRQL	Health related quality of life
HTD	Hospital of Tropical Diseases
IBM	Individual-based stochastic mode
ICER	Incremental cost-effectiveness ratio
IEC	Information &education& communication
IMF	International Monetary Fund
IQR	Interquartile range
IRIS	Immune reconstitution inflammatory syndrome
K13	The Kelch13
KMSA	Kaplan-Meier sample average
LLIN	Long lasting insecticidal nets
LIC	Low income countries
LMIC	Low middle-income countries

M/M&E	Program management, monitoring, and evaluation
MAR	Missing at random
MCAR	Missing completely at random
MDR-TB	Multiple drug resistance
MeSH	Medical subject Headings
MFT	Multiple first-line therapies
MI	Imputation analysis
MICE	Chained Equations
MLICs	Middle and low-income countries
MNAR	Missing not at random
Mtb	Mycobacterium tuberculosis
NMB	Net monetary benefit
NPV	Nevirapine
OIs	Opportunistic infections
OOP	Out-of-pocket
OUCRU	Oxford University Clinical Research Unit
PCP	Pneumocystis jirovecii pneunonia
PEPFAR	U.S President’s Emergency Plan for AIDS Relief
PNT	Pham Ngoc Thach hospital
QoL	Quality of life
QALYs	Quality adjusted life years

R0	Basic reproduction number
RR	Relative risk
SAPIT	Starting antiretroviral therapy at three points in tuberculous patients
SE	Standard errors
SP	Sulfadoxine/pyrimethamine
SSRN	Social Science research network
SSA	Sub-Saharan Africa
STRIDE	Strategy study of Immediate versus deferred initiation of ART for HIV-infected persons treated for TB
TB	Tuberculosis
TB-HAART	Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis
TBM	Tuberculous meningitis
TDF	Tonofovir
TIME	Time to initiate antiretroviral therapy between 4 weeks and 12 weeks of tuberculosis treatment in HIV-infected patients
TTO	Time trade off
UIC	Upper income countries
VAS	Visual analog scale
VMW	Village malaria workers

WHO	World health organization
WHO-CHOICE	WHO Cost-effectiveness and strategic planning
WTP	Willingness to pay
YLD	Years of life lived with disability
YLLs	Years of life lost

Currency

USD	US Dollars
VND	Vietnamese Dong

Chapter 1

Introduction and aims of the thesis

1.1 Main aims of the thesis

My DPhil thesis has two main aims:

1. To determine the costs and cost-effectiveness of immediate versus deferred antiretroviral therapy in Human immune deficiency (HIV) infected patients with tuberculous meningitis (TBM) in Vietnam;

2. To determine the costs and cost-effectiveness analysis of multiple first-line therapies (MFT) to delay drug resistance evolution in malaria

1.2 Overview of health care and health financing in Vietnam

Vietnam is a South East Asian country, bordering China to the north, and Laos and Cambodia to the west (Figure 1.1). The estimated total population of Vietnam in 2015 was 94.3 million. About 24.5% of the population was in the aged less than 15 years, and 6.4% aged more than 65 years or more. The healthcare administration in Vietnam is organized into a three-level system: tertiary level (Ministry of Health), provincial level (63 provinces) and primary level (698 districts, and 11,121 communes). The gross domestic product (GDP) of Vietnam in 2015 was 193 billion or $2,110 per capita (2015 USD) (Table 1.1). This is a monetary measure of the market value of all final goods and services produced within a country's borders by both its own citizens (and companies) and foreign ones residing in this country within period of time (yearly or monthly). The GDP reflects the performance of the

economy from year to year [3]. Gross national income (GNI) is similar as GDP but takes into account of the flow of income in and out of the country. Total health expenditures in Vietnam has been increasing rapidly from 4% of GDP in 2004 to 7% of GDP in 2014. The estimated per capita health expenditures in Vietnam has increased from $63 per year in 2008 to $142 by the end of 2014 [4], more than twice the level in 2008 (Figure 1.2). Vietnam's current spending reflects positive healthcare policy reforms during the past few years. However, an increasing cost burden has also been created because Vietnam is beginning to shoulder a double burden as it still has high rates of infectious disease but also more Vietnamese people are being diagnosed with treatable long-term chronic diseases. Second, the economic growth is widening the gap between rich and poor people in many aspects, including health care utilization [5]. The public hospitals tend to be overcrowded has poor quality of care [6]. While the health system faces rising costs and dwindling resources, the international funding is starting to decrease, as Vietnam has just reached the lower middle-income level. The Vietnamese government now faces the tremendous challenge needs to improve the health system for accountable, equitable and efficient use of limited health funds to ensure sustainable resource allocation in the future. General economic and health indicators are shown in Table 1-1 and Figure 1.1.

Figure 1-1: Vietnam map. Ho Chi Minh City is highlighted in yellow.

The capital of Vietnam is Ha Noi, in the northern part of this map.

Table 1-1: Economic and health indicators in Vietnam

Key Indicators	
Population (2015)	94.3 million
Per capita gross domestic product (2015,current USD)	$2,111
Income classification	Lower-middle
Health financing (2014)	
Total health expenditure per capita (USD)	$142
Total health expenditure as % of gross domestic product	7%
Out-of-pocket as % of total health expenditure	36.7%

Source: World Bank 2016 [4]

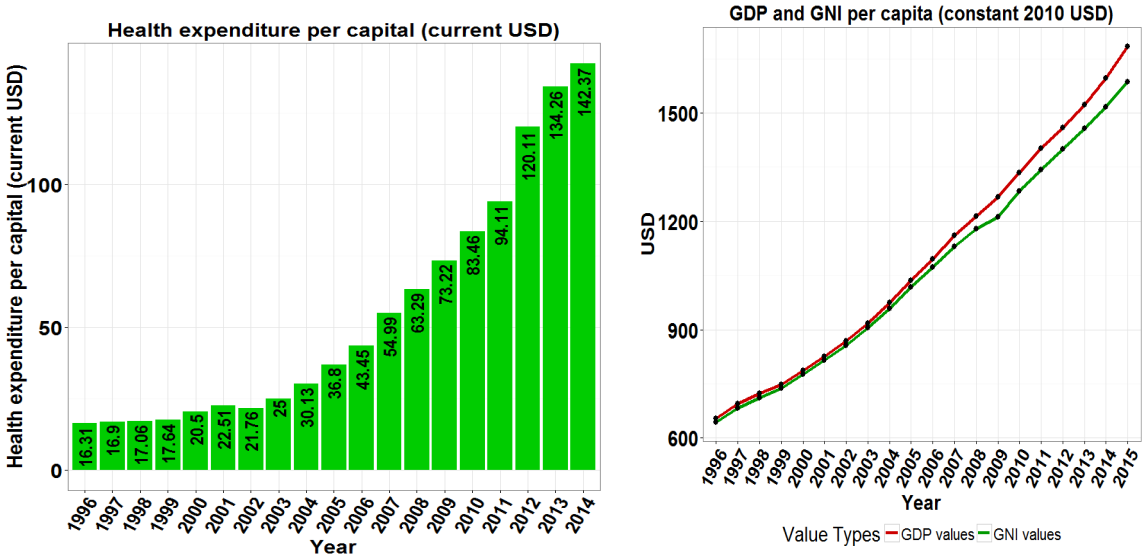


Figure 1-2: General economic and health indicators in Vietnam. The first graph illustrates the health expenditure per capita (y-axis) from year 1996 to year 2014 (x-axis). The second graph presents the GDP and GNI per capita (y-axis) from year 1996 to year 2014 (x-axis). Data sources were from World Bank 2016 [4]

1.3 **Overview of economic evaluation**

1.3.1 **Introduction to economic evaluation and priority setting in health care**

Economic evaluation is a branch in health economics that guides decision makers to make choices regarding the allocation of limited healthcare resources, and enables them to be used efficiently to maximize social and economic benefits [7]. Little work had been done on the economics of health prior to 1963. During this period, one distinctive piece of work from Milton Friedman studied differences in inequality of incomes between dentists and physicians and other jobs[8]. However, his work could hardly be considered as a discipline of health economics that addressed the issue of scarcity in the allocation of healthcare. Economists began to establish interest in health issues at the beginning of the 1960s. The earlier work of Kenneth Arrow[9]has made fundamental contributions to healthcare, which concentrated around general equilibrium theory and welfare economics. Welfare economics is concerned with the well-being of the individuals at the aggregate (society) level [10]. Since the 1960s, there has been a remarkable explosion in health economic research in various diseases due to the emergence of many new therapeutic treatments.

A widely accepted definition of economic evaluation is the "*comparative analysis of alternative courses of action in terms of both their costs and consequences*"[11]. Costs are the value of resources associated with a treatment or interventions, including resources such as people, time, and knowledge[12]. Consequences can be

considered as the health effects of the intervention on people's well-being or health status. The objective of economic evaluation is to allocate the resource in society as efficiently as possible to maximise human welfare or utility [13].

1.3.2 **Types of economic evaluation**

The four techniques that have been applied most commonly in the health sectors to assess the efficiency of health services, are cost-minimization analysis, cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). The measurement of costs in monetary units is similar across most economic evaluation. The different ways of measuring benefits result in a trade-off between the potential scope for use and the practicality of various evaluation techniques [14].

1.3.2.1 Cost-minimisation analysis

Cost-minimization analysis is appropriate for the comparison between alternative interventions for the same disease where the alternatives have been proved to have equivalent outcomes. The health intervention, which are the least costly, is the most efficient. The advantage of this analysis is to provide the assessment of costs incurred to develop and implement an intervention. The major weakness of the cost-minimization analysis is that it is rare to find treatment options that yield identical outcomes. The reported results might ignore some other outcomes such as the relapse rate, which might differ between the two treatment [15,16]. This approach is not relevant for the policy makers who are interested in the joint distribution of the costs and effect differences [17].

1.3.2.2 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is one form of full economic evaluation. The analysis is more flexible tool than cost- minimisation because it considers at interventions (on the same disease) in which the benefits and costs of alternatives differ . In CEA, the health benefits are measured usually using a single outcome, in "natural" units. The health outcomes are expressed as intermediate outcomes such as cases averted or the number of children fully immunized by vaccination programs, or final outcomes such as effectiveness such as life-years gained [16]. The summary measure for CEA is the incremental cost-effectiveness ratio (ICER) which compares the costs and effectiveness of a given intervention to the costs and effectiveness of another effective intervention. Cost-effectiveness analysis is recommended for comparing interventions that address the same health problem[18].

There are some limitations for the CEA approach. Firstly, the intermediate outcomes (e.g. the number of people who stop smoking) are assumed to be linked to outcomes (improve life expectancy). However, establishing the correlation between intermediate and final outcomes is not an easy task, which sometimes requires the use of mathematical modeling. A second limitation of intermediate outcomes is that the health benefits gained are often disease-specific and not comparable across different interventions. Alternatively, using final outcome indicators such as the number of lives or years of life saved by health program are more flexible to compare across different types of treatment but only reflect one aspect of health which aimed at saving lives, ignoring the morbidity[16]. Allowing

for only one aspect of benefit to be compared can provide a misleading picture of health benefits

1.3.2.3 Cost utility analysis

Cost-utility (CUA) is another form of cost-effectiveness analysis which combines the impact of interventions on both mortality and morbidity into a single outcome indicator [15]. The health outcome indicator of the CUA is expressed most commonly in terms of quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). These outcomes are used in cost-effectiveness studies to enable comparisons to be made across therapeutic areas, with the QALYs or DALYs acting as the 'common currency'. Results of CUA are typically expressed as cost per QALY saved or DALY averted. The QALY concept combines the survival of an individual with their health related quality of life (HRQL). Over time, individuals experience different health states, where the health states are adjusted according to the HRQL weight (i.e. utility score) associated with them. HRQL weights reflect the value individuals place on the quality of life experienced during the treatment period in terms of a consistent set of health dimensions such as physical function (mobility and physical activity); role function (self-care and role activities); social-emotional function; and the nature of the health problem. The CUA has been commonly used in health sectors to assess the interventions against the assumed policy-makers' willingness to pay thresholds for the incremental benefits. However the CUA based on the thresholds has also experienced other problems, which are discussed later in the thesis. Many researchers for instance have questioned the appropriateness of different types of

HRQL measures that are used in CUA. Some measures are based on general improvements in health (generic measures), and others are based on disease-specific health improvements. Such differences can make it difficult to compare one QALY with another.

The following section discusses the strengths and weakness of the use of DALYs and QALYs in developing countries:

DALYs and QALYs are two summary measures of effectiveness that are perceived as valid summary measures of effectiveness in economic evaluation [19]. They both have advantages of using a single indicator to measure the effectiveness of health-care interventions in terms of the impact on life expectancy and quality of life [20] that would facilitate comparison of the health problems across disease types and between countries [21].

The weaknesses of the use DALYs and QALYs in developing countries are that most studies in these countries did not use country-specific valuations of health states. It is known that the calculation of QALYs required utility weights to adjust the patient's survival for different states of health [27]. Ideally utility weights could be derived from the preferences of a general population of the country where the weights were to be used. However, Kularatna (2013) [28] identified very few EQ-5D studies in LMICs (n=5) that used their respective country population tariffs for utility weights. The other studies had valued utility weights for EQ-5D using preferences of people from Western Europe which was socially and culturally different. Moreover, several researchers have mentioned that utility scores of QALYs were often developed with small, non-representative population sizes [29].

Thus, the paucity of utility weights using country-specific preferences in LMICs could give a misleading result of CEA [24].

The same as QALYs, most applications of DALYs did not use country-specific valuations of health states [24]. In line with this argument, Nord (2015) [30] have raised concerns that disability weights given in the GDB did not reveal a clear description of how valid they were for use in populations that may differ regionally and economically, from those from which they were derived.

Some critics considered that DALYs and QALYs were unsuitable approach in evaluating health outcomes of complex interventions, such as integrated case management of HIV, malaria and diarrhoea in Kenya [31] and mental health [32]. Complex interventions such as integrated case management often had a range of outcomes which were inadequately captured by QALYs and DALYs. Moreover, some other authors questioned validity and the ability of DALYs and QALYs to measure the value of interventions for acute conditions and co-morbidities [33]. All these issues of DALYs and QALYs above were commonly applicable to developing countries [34–36].

1.3.2.4 Cost-benefit analysis

Cost-benefit analysis (CBA) takes into account all costs and health effectiveness associated with an intervention expressed in monetary terms[37]. Both costs and

effectiveness are discounted to their present values. Discounting is a method used to make the value of costs and benefits comparable regardless of timing they incur [38]. The two most commonly used summary measures for CBA are net benefits (present value of benefits minus present values of costs) and benefit-cost ratio (present value of benefits divided by present value of costs). If the benefit-cost ratio is greater than 1 or the net benefit is greater than 0, the program is considered worthwhile taking, subject to budget constraints. The advantage of this method is that it tends to take into account of all possible benefits of an intervention (such as non-health effects: the increased value of infrastructure) and the funders found it easy to identify and judge the value for money of certain interventions.

However, the CBA also contains some problems. In particular, it has been difficult to convert health benefits, such as lives saved, into monetary terms. The most common way of measuring benefit in monetary units that underline with economic theory is to use the concepts of willingness to pay (WTP). WTP estimates are usually obtained from hypothetical questions for people about what they would be willing to pay to reduce the disability or to gain an improvement in the quality of life, a technique known as contingent valuation (CV). This form of CBA makes no adjustment for unequal distributions of income or health. Richer people can pay more and would demand different types of health services to the poor, and the health system is likely to be driven by the demands of the rich.

Determining appropriate framework depends on several factors such as the costing perspective, the types of costs being included and so on. Recognizing the limitations and the advantage of each framework, CEA and CUA will be used in

the thesis to allow diverse health outcomes to become a common unit that facilitates comparison across interventions and diseases. The CBA approach is not considered appropriate because converting the health benefits to monetary values has been subject to great debate. The step-by-step framework for conducting these techniques is presented in chapter 3, and chapter 5.

1.3.2.5 Some considerations of economic evaluation

Economic evaluation methodologies have been improved over the past 10 years to cover specific areas such as modeling and extrapolation methods, and evaluation alongside clinical trials. Nevertheless, economic evaluations are still subject to methodological limitations. The most controversial issues have been the threshold for decision makers to determine whether the intervention is good value for money. The widely used maximum willingness to pay to avert a disability adjusted life year (DALY) is by reference to a country's GDP per capita. The WHO has recommended that interventions with an ICER less than the country's GDP can be considered cost-effective, and those with a ratio greater than three times GDP should be considered not cost-effective[39]. A willingness-to-pay threshold represents an estimate of what a consumer of healthcare is willing to pay per unit of effectiveness given other competing demands on that consumer's resources[40]. The conceptual foundation and derivation of these thresholds were described in this paper [41]. Williams (2004) [42] was in support of the WHO GDP based thresholds arguing that each person has an entitlement to a 'fair share' of the

country's wealth and that this can be approximated by average national product per person.

The reasons why the WTP thresholds were recently revised and discussed extensively in [40,41,43], two main issues can be identified. First, it has been argued that these GDP based thresholds are too simply derived and are based on untested assumptions [43] which could lead to inappropriate conclusions regarding which interventions should be adopted as well as misallocation of resource within the health system and healthcare inequalities. There appears to be no empirical or theoretical basis behind these benchmarks [44]. In the Bulletin of the WHO 2014, Marseille et al (2014) [43] argued that there was little evidence regarding the linear relationship between the willingness to pay for health and income and other factors could determine willingness to pay such as the budget and technical capacity of a national malaria control programme. In addition, several authors argued that the use of a cost-effectiveness threshold based on a country's per capita GDP gave a biased measure of the willingness to pay because DALY averted were valued more highly in high-income countries than in low-income countries [45]. These thresholds were considered too strict in high income countries where more effective interventions would be ruled out and too easy in low-income countries, where some ineffective options might be adopted. GDP –based cost effectiveness thresholds became problematic when making cross-country comparisons [46].

The second limitation, GDP based thresholds fail to assess information on affordability, budget impact or the feasibility of implementation [40]. These thresholds omit any consideration of what is truly affordable within a particular context. For example, in HIV treatment adding methadone to a package of interventions would be cost–effective – i.e. cost less than three times the per-capita GDP per DALY averted. However, the costs of adding methadone would have exceeded Vietnam's entire budget for HIV treatment [47].

Decision makers are not only interested to know that the costs per DALY averted of an individual intervention is less than 3 times the local annual per capita GDP, but also whether it costs less per DALY averted than other feasible interventions [49]. Thus, there has been some suggestion of having multiple thresholds for different patient groups or circumstances[12]. Bertram et al (2016) [40] suggested from their research experience that countries should consider establishing WTP based thresholds that were suitable for the local decision making process that is supported by legislation, has stakeholder buy-in and is consistent, fair and transparent.

Economic evaluation has yet to be widely and rigorously used to evaluate different interventions in healthcare decision making in LMICs[10]. A common challenge is the scarcity, quality and accessibility of data, which is caused by the insufficiency of routine cost accounting system, limited patient-information systems [33,50] and limited funding for health economic research capacity. A growing body of general and disease- and intervention-specific guidelines on economic evaluation in health

care[12,51]has developed an international “reference case” to facilitate comparison across cost-effectiveness studies. These guidelines are mainly applicable for high income countries and show the various methods for measuring costs and benefits [52].

1.4 **Health economic research in Vietnam:**

Health economics is an emerging area in Vietnam; therefore evidence from economic evaluation research is greatly limited. The growing literature in this field started in 2010 when the Vietnam Health Economics Association (VHEA) was set up. I conducted the keywords search “cost-effectiveness analysis in Vietnam” in PubMed that yielded 25 studies, mainly of HIV and rotavirus interventions (8 studies) and vaccines (5 studies) (Table 1.2).

Table 1-2: Number of cost-effectiveness studies in Vietnam in PubMed

Publications	**Number**
Haemophilus influenza type b vaccine	1
Expantpded immunization	1
Schizophrenia interventions	1
HIV (earlier ART & methadone)	4
Cryptococcalantigenemia screening	1
Malaria: LLIN hammocks	1
Cleft lip and palate	1
Brain metastasis	1
Rotavirus immunization, vaccines	4
Reproductive health: iron folic acid	1
Tobacco control policies	1
Screening blood donors	1
Cervical cancer screening	1
Cardiovascular disease	1
Oral cholera vaccine	1
Typhoid Vi vaccination	1
HPV vaccination	1

Hepatitis B vaccination	1
Papanicolaou cytology screening	1
Total	**25**

Thi, My, & Thanh (2014) identified 18 CEA studies in Vietnam that followed the criteria set out in Drummond's 10 point checklist evaluating the quality of CEA studies [11]. The review found that there was substantial variation in economic evaluation methodology and quality, reducing the credibility of such studies to usefully inform decision-making in health. Fourteen out of the 18 suggested that the intervention/programs/treatments they were evaluating would be cost-effective if implemented.

This review shows that economic evaluations in Vietnam were limited and of poor quality. Based on the principles of Drummond guidelines[53], these findings of this review highlight a couple of current challenges in the use of economic evaluations in Vietnam. Four common themes emerged when exploring the gap in the methods among economic evaluations in Vietnam, namely:

First, none of the health economic studies were based on reliable data sources from randomised controlled trial. This review highlighted the lack of trial-based economic evaluation and economic evaluations of drug resistance. Costs and consequences did not value credibly. Around 70% of studies did not capture or properly compute the productivity losses. This information called into question the quality of data being used by the current research (Figure 1-3).

Second, most of the model-based studies evaluated over a short time horizon (1 year) and did not incorporate the issues of antimicrobial resistance [54]. The majority of prevention CEA studies applied a Markov model to calculate the cost-effectiveness ratios. Thi, My, & Thanh (2014) criticised that some of the model-based studies did not incorporate the evaluation of uncertainties such as examining the model's robustness by probabilistic sensitivity analysis, or checking the potential uncertainty of cost data by sensitivity analyses.

Third, Vietnam lacks decision-making institutions and formal health economics. Almost 80% of the papers published in Vietnam did not report using any health economics guidelines for their studies [2]. Another technical limitation were that just over a third of the published economic evaluations did not explain why particular comparators were chosen for the analysis and how the specific costing methods or the health outcome measurements were selected to answer the economic problems of the study. Many of the technical limitations in the published studies could be resolved if these studies complied with cost-effectiveness analysis guidelines such as a the international CHEERS (2016) [53] to guide future evaluations, and improve both the consistency and usefulness to decision makers .

Finally, the lack of clarity in many of the papers' descriptions of methodology and results may have impaired our process of understanding the quality (Figure 1-4). Most papers did not argue whether there exist any missing data and how they tackled these missing values in costs, effects and then in acceptability curves. Therefore there is a need to enhance research capacity in health economic

evaluation in Vietnam to ensure that Vietnamese researchers have the capacity to produce high quality health economic research aligning with the local political context and culture, and thus likely to be relevant to the local policy makers.

To reduce this research gap, my DPhil research conducted two economic evaluations, one trial-based and one model-based, which will be of substantive importance as estimates of the cost-effectiveness of different health interventions in treating HIV/TBM and malaria in Vietnam. They will also act as case studies to demonstrate their relevance of health economics to health care decision making in the context of a developing country like Vietnam.

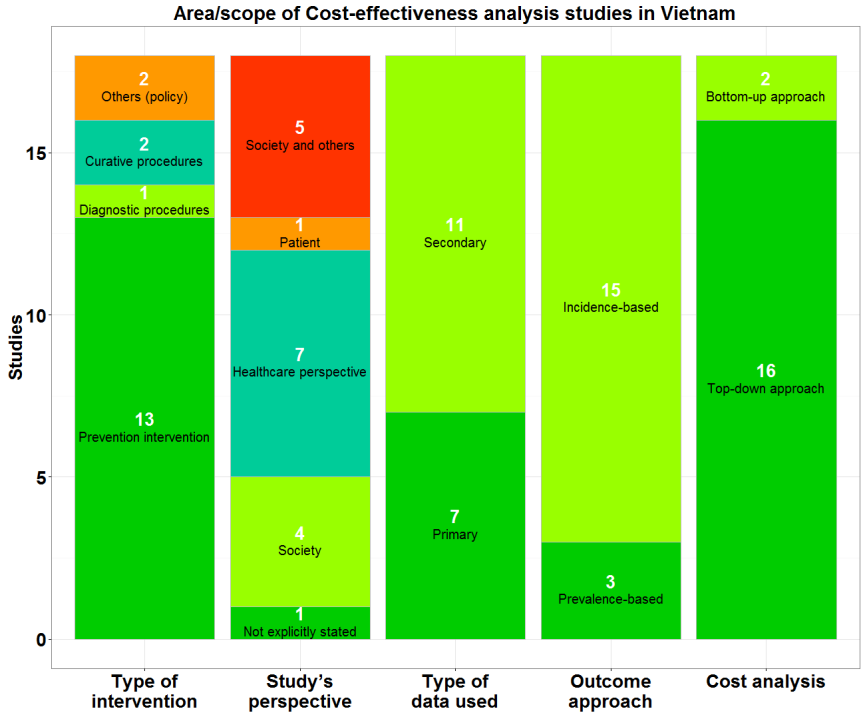


Figure 1-3: Scope of cost-effectiveness analysis studies in Vietnam (data extracted from My et al (2014) [1])

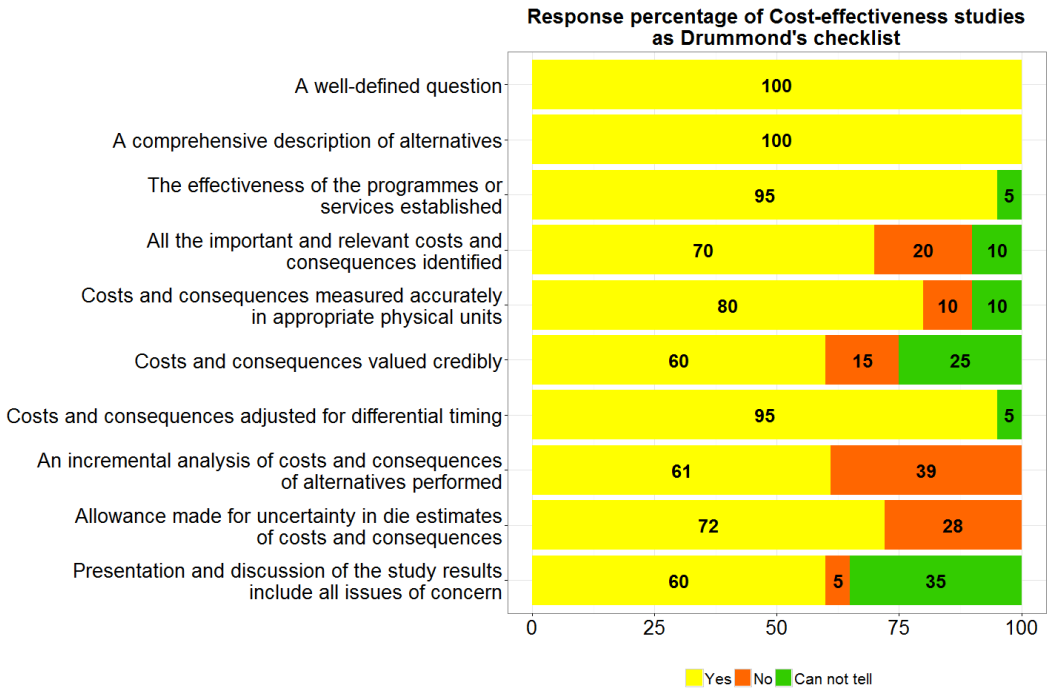


Figure 1-4: Quality of cost-effectiveness studies according to Drummond's checklist (data extracted from My et al (2014) [1])

1.5 **Background of the HIV/TBM project**

It is estimated by WHO that tuberculosis (TB) affects one third of the world's population, of which approximately 10% will develop clinical disease [55]. Tuberculosis, due to infection with the bacterium Mycobacterium tuberculosis, can occur in anybody system. Most commonly, it is the lungs that are affected. However, the most serious form, affecting around 5% of those who develop disease, is tuberculous meningitis, where the organism primarily infects the brain and the membraneous lining of the brain (the meninges). While TBM can occur in people with normally functioning immune systems, it is particularly severe in patients infected with Human Immunodeficiency Virus (HIV)[56]. These patients are generally significantly immunosuppressed with profoundly low CD4 cell

counts. The CD4 cells are the cells of the immune system that coordinate the immune response and which are particularly affected by HIV. In Vietnam, mortality for the TBM grade groups in our trial of immediate versus deferred antiretroviral therapy (ART) for HIV-associated adult TBM was grade I, 40%, grade II, 52% and grade III, 75% [57]. (The TBM grade is explained in the Appendix 2).

Antiretroviral therapy directed against HIV has had a dramatic effect in improving survival in patients with HIV. However, treatment can be difficult to take and has significant side effects, and until recently it was not clear whether ART should be started at the point of HIV diagnosis, or should be delayed until there was evidence of immune damage. Recently it has been shown that it is advantageous to start ART as soon as possible, irrespective of CD4 count. In patients presenting to health services severely unwell with opportunistic infections such as TB, it has been less clear when to start ART. The potential benefits of immune system improvement due to starting ART must be balanced against the increased complexity of treatment regimen, side effects, drug interactions, possible adverse effects of immune reconstitution and costs. Currently WHO guidelines recommend that antiretroviral therapies (ART) should be started in all TB patients living with HIV regardless of the CD4 count. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/μL the median level in patients with HIV and TBM being around 30 cells/ul) should receive ART within the first two weeks of initiating TB treatment(Section 4.3.5

[58]. These guidelines were based on the results of HIV and TB trials [59–61] that examined whether to commence ART immediately or once a patient was established on TB medication. These retrospective studies have shown that starting ART early in severely immunosuppressed patients with TB was associated with decreased mortality and a lowering of rates of progression; however, the studies are notable because few of the patients within them had TBM. Thus, the WHO acknowledged the limited evidence on the impact of antiretroviral drugs in HIV-associated TBM and warranted caution as immediate ART was significantly associated with more severe adverse events when compared with initiation of ART two months after the start of TB treatment. This conclusion is based on data from the randomized, double blind, placebo-controlled trial of immediate versus deferred ART in HIV-infected patients presenting with TBM at two public hospitals in Vietnam [57]which found that there was no difference in mortality between patients receiving immediate versus delayed therapy (hazard ratio [HR], 1.12; 95% confidence interval [CI], 0.81 to -1.55; P =0.50).

The objective of the first part of my DPhil is to conduct an economic evaluation of immediate versus deferred ART in Vietnamese HIV-infected patients with TBM using the data from this trial [62]. I will focus on estimating the incremental cost-effectiveness ratio (ICER) - expressed as cost per QALY gained of immediate ART versus the deferred ART.

1.6 **Background of the malaria project**

Artemisinin resistance has become a threat to public health care in South East Asia. One of the strategies to slow artemisinin resistance might be the introduction of multiple first-line drugs. Nguyen and colleagues [63] developed an individual-based microsimulation of *Plasmodium falciparum* malaria that compared 3 different treatment strategies at national level to examine which strategy could be applied as widely as possible without accelerating the erosion of the drug efficacy by drug resistance. The first strategy is the "Cycling strategy", defined as where the national first-line drug policy changed every 5 years. In the "Sequential strategy", the national first-line drug policy changed everytime the percentage of treatment failures reached 10% in the population with an assumed 1-year delay. The third "MFT strategy" is defined as where multiple first-line drugs were distributed at onetime in the population and therefore no policy change occurs over time.

The objective of this analysis is to assess the long-term costs and cost-effectiveness of an MFT strategy as compared with either sequential or cycling policies using a dynamic stochastic simulation model of the epidemiology of *Plasmodium falciparum*. In particular, the study estimated the incremental costs and health gains (DALYs averted) of implementing the MFT strategy as compared with the single first-line therapies to explore whether this therapy was a cost-effective strategy to reduce *P.falciparum* malaria disease burden under different scenarios of *P.falciparum*biology and epidemiology.

1.7 **Contributions to the existing knowledge**

The research undertaken and reported in this thesis aims to develop a framework for how to perform cost effectiveness research for HIV and malaria treatment in low-income countries such as Vietnam, and to make this available to policy makers in Vietnam. This thesis is going to contribute to a growing literature on economic evaluation in infectious disease in Vietnam and in general in middle and low-income countries. The work utilises the unique datasets generated by OUCRU and collaborators on TBM and malaria.

1.8 **The structure of the thesis**

Following the introduction, this thesis will discuss the economic evaluation results of these two above studies, including issues surrounding the generalizability of findings and the interpretation of cost-effectiveness results. Based on the main aims, the structure of this thesis is structured as follows:

Chapter 2: HIV/TBM literature review. This chapter presents a systematic review of studies that assessed the optimal timing of antiretroviral therapies to treat HIV and TB patients.

Chapter 3: Methodology and results of HIV/TBM cost-effectiveness study. This chapter outlines the step-by-step analytical approach, the cost-effective results based on the patient-level data from HIV/TBM trial and the interpretation of this study's findings, limitation and inherent assumptions.

Chapter 4: Malaria literature review. This chapter provides a systematic review of the costs of antimalarial drug policy change and the costs of antimalarial drug procurement delivery, both of which will inform the economic evaluation of implementing multiple first-line therapies to treat *P.falciparum* malaria.

Chapter 5: Methodology and results of malaria cost-effectiveness study. This chapter comprises the main results of employing multiple first-line drugs to treat malaria, as compared with the cycling and sequential strategies, a discussion and the implications of these findings for current and future action.

Chapter 6: Final discussion, conclusions and further recommendations. This chapter highlights the comparative strengths and weakness of conducting economic evaluation alongside randomized clinical trial, followed by the discussion of issues relating to the economic evaluation using decision-modeling framework. This chapter concludes the thesis with some thoughts on how continue this work, and possible further work to address the more complicated methodological issues. Additional information, including descriptions of my methodology and data sources is presented in appendices annexed to this report.

Chapter 2

Literature review for the cost-effectiveness of optimal timing of antiretroviral therapy in HIV/AIDS patients associated with tuberculous meningitis

2.1 Overview of human immunodeficiency virus associated tuberculous meningitis in the world and in Vietnam

2.1.1 Clinical background on tuberculosis meningitis and human immunodeficiency virus associated tuberculous meningitis

Tuberculosis(TB) is disease due to infection with *Mycobacterium tuberculosis*(Mtb). Mtb is a small gram positive bacterium identified by Robert Koch in 1882. This bacterium is resistant to decolorization by acid and alcohol during diagnostic staining procedures (‘acid and alcohol fast’). TB disease can occur in any tissue, but the lungs that are most frequently affected (pulmonary TB). Disease elsewhere is classified as extrapulmonary TB. Tuberculous meningitis (TBM) occurs when Mtb causes infection of the meninges— the covering of the brain and spinal cord, along with infection of the brain parenchyma and/or spinal cord itself. TBM is the most severe form of infection with *Mycobacterium tuberculosis* [64,65].TBM is diagnosed into three different categories: definite, probable, or possible (Appendix 1).

A randomized, placebo-controlled trial of adjunctive dexamethasone treatment in Vietnam demonstrated that HIV-associated TBM patients (96 individuals) had a

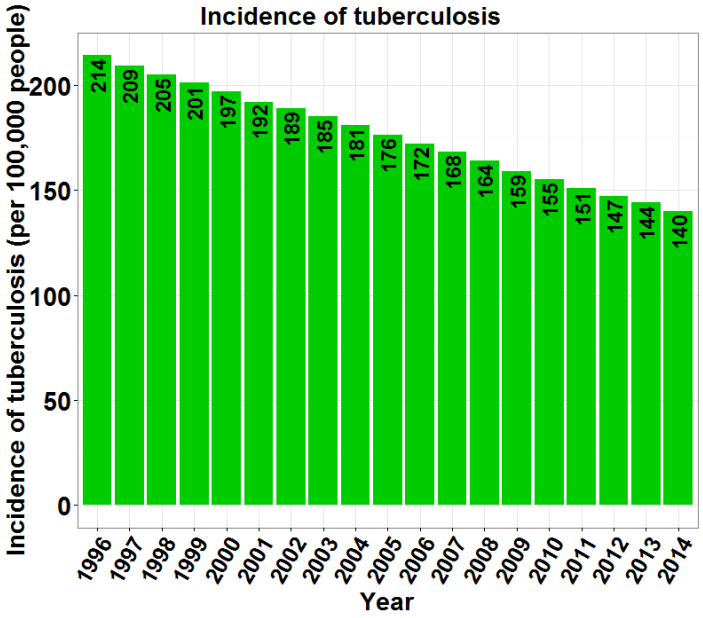
similar clinical presentation but higher mortality compared with HIV-negative patients(432 individuals) [66]The pattern of neurological deficits was similar between groups, HIV infected patients were more likely to have other organ involvement and the 9 month mortality rate was significantly higher (relative risk of death from any cause, 2.91 95% CI 2.14 to 3.96; p<0.001). The relapse rate and the adverse events were similar in the two groups.

In a further study from Vietnam, a prospective, observational cohort study was conducted to determine the clinical and microbiological features in HIV-TBM adult patients [56]. Fifty-eight patients were recruited to the Hospital for Tropical Diseases in Ho Chi Minh City from November 2004 to September 2005.These patients received standard antituberculous therapy and adjunctive dexamethasone, ART was not routinely available. This study found that the majority of HIV-TBM patients had grade III (severe) TBM at presentation, with Glasgow coma scores (GCS) less than 10. All patients had CD4 counts ≤200 cells/uL and frequent other clinical features of HIV infection, including generalized lymphadenopathy, oral candidiasis and herpes zoster. CD4 cells are key components of the human immune system, important in organizing and coordinating the immune response. A CD4 counts ≤200 cells/uL indicates extreme immunosuppression and is sufficient to make the diagnosis of Acquired Immunodeficiency Syndrome (AIDS).

2.1.2 **HIV/TB epidemics in the world and in Vietnam**

In 2013, 9 million people were infected with tuberculosis (TB) and around 90,000 to 100,000 people will develop tuberculous meningitis each year (1% of TB population) [55]. The WHO has not reported data on HIV/TBM specifically. In

Vietnam, an estimated 220,846 people were living with HIV at the end of 2014 [67] and 102,070 new TB cases were reported in 2014. An estimated 3,875 people were co-infected with HIV, of whom 2,232 were receiving antiretroviral therapy (ART). Among these HIV/TB cases, an estimated 797 individuals would have had extra-pulmonary TB. Ho Chi Minh City has the highest burden of HIV/TB (1,360 patients) and HIV-extra-pulmonary TB (312 patients) in Vietnam [68] (Figure 2-1). There is no accepted published estimate of the total prevalence of HIV-TBM in Vietnam, but according to the interview with doctors at Hospital of tropical diseases (HTD) in Ho Chi Minh City, approximately 400 HIV-TBM patients were admitted to this hospital each year. The number of HIV-extra-pulmonary TB infected patients in the national TB report is likely to be underestimated as not all patients presenting with TB may be tested for HIV. The true incidence rate of HIV-extra-pulmonary may be about 2 or 3 times higher than reports have indicated. More accurate estimates of HIV-TB stratified by severity of TB are needed to clarify this issue.


Incidence of tuberculosis
Incidence of tuberculosis (per 100,000 people)
0
50
100
150
200
214
209
205
201
197
192
189
185
181
176
172
168
164
159
155
151
147
144
140
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
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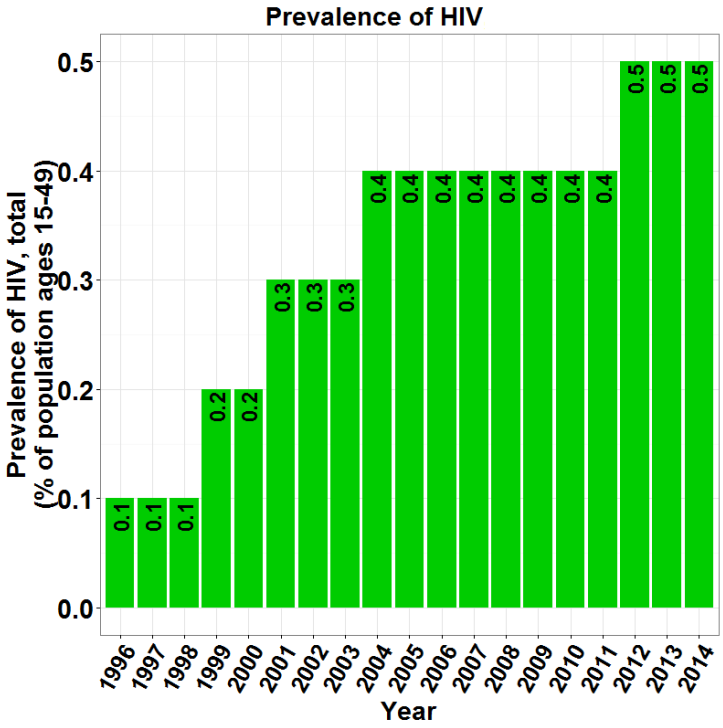

Prevalence of HIV
Prevalence of HIV, total
(% of population ages 15-49)
0.0
0.1
0.2
0.3
0.4
0.5
0.1
0.1
0.1
0.2
0.2
0.3
0.3
0.3
0.4
0.4
0.4
0.4
0.4
0.4
0.4
0.4
0.5
0.5
0.5
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year

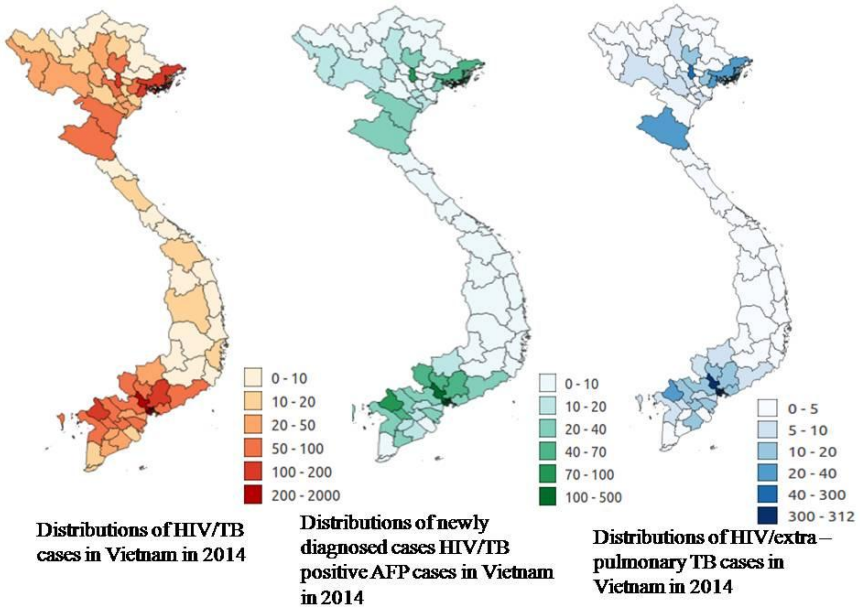


Figure 2-1: The first figure illustrates the annual incidence of TB cases per 100,000 people (y-axis) from year 1996 to 2014. The second figure represents the annual prevalence of HIV as percentage of population of ages 15-49 (y-axis) from the year 1996 to 2014 (x-axis). The third figure presents the geographical distribution of HIV/TB cases in Vietnam in 2014 which were obtained from national TB control in Vietnam [68].

2.2 **Clinical background on the optimal time point to initiate ART in HIV-infected patients in general**

Since the introduction of zidovudine (AZT) in 1987, significant advances in antiretroviral therapy have been made. Nowadays, standard ART consists of the combination of at least three antiretroviral (ARV) drugs. The ART is effective in reducing the HIV viral load in the body, which allows an immune recovery. Since 2010, increasing evidence also indicates that initiating ART earlier reduces non-AIDS defining conditions. Nevertheless, how early ART should be started is still debated. In 2016, WHO recommends that ART should be initiated in all adults

living with HIV, regardless of WHO clinical stage and at any CD4 cell count which was supported by moderate-quality evidence [58].

In Vietnam, the Ministry of Health had standardised the national guidelines for diagnosis and treatment of HIV/AIDS in 2005 [69]. These guidelines allowed patients to receive free antiretroviral drugs and free tests for CD4 counts during their treatment. The Vietnamese national guidelines for HIV treatment have been updated three times since 2005 (in 2009 and 2011 and 2015). The latest guidelines (2015) suggested initiating ART when the CD4 counts were less than 500 cells/uL. Since 2011 the preferred national first-line ART regimens have been TDF (Tonofovir) + 3TC (lamivudine) + EFV (efavirenz)/NVP (Nevirapine). Representatives of the Vietnam Administration of HIV/AIDS said that they are aware of the new guidelines from 2016 from WHO, but the new guidelines have not yet been implemented in Vietnam.

2.3 **Clinical background on the optimal time point to initiate ART in HIV-infected patients and tuberculosis**

Most guidelines do not recommend giving simultaneous initiation of ART and anti-TB medications because there are concerns over the competing risks of starting early ART. The dilemma concerning early versus late ART can be summarised as follows:

Advantages of early ART:

- Early immune reconstitution which

    - Reduces the risk of additional opportunistic infections (OIs) developing
    - Improves immune function and therefore recovery from the current OIs
- Get the patient established on ART in hospital early – perhaps better adherence

Disadvantages of early ART:

- Increased expenses
- High pill burden which could affect adherence to both treatments
- Increased risk of drug side-effects (adverse effect)
- Drug interactions which make the ART or the OI treatments ineffective or toxic to the body, as toxicity is higher compared to treatment of each infection separately
- IRIS – immune reconstitution inflammatory syndrome – describes a paradoxical worsening in the patient's disease state as the immune system's function improves due to ART. This is because immune reconstitution is associated with increased inflammation, which results in worsening of the patient's symptoms. It is possible that the effects of IRIS may be particularly severe in brain infections. The risk of IRIS is higher in patients with rapid increase of CD4 and/or rapid decline in viral load, and can be severe and even life-threatening [70].This may be especially true in brain infections.

The current WHO guidelines for TB treatment [58]recommend that HIV patients co-infected with tuberculosis should start ART as soon as possible within 8 weeks of starting tuberculosis treatment (and that those with CD4 counts ≤50 cells/uL should receive ART within the first 2 weeks). However, the optimal time to initiate ART remains contentious with regards to other forms of TB, such as TBM. I will now give a brief summary of the results of the key trials examining the timing of ART in active tuberculosis.

SAPIT (2010) [60](Starting antiretroviral therapy at three points in tuberculosis) was a randomized clinical trial performed in South Africa from 2005 to 2008. 642 HIV-infected treatment-naive patients with CD4 cell counts ≤500 cell/uL and smear-positive pulmonary TB were included. HIV/TBM patients were not specified in this trial. The median baseline CD4 cell count was 150 cells/uL. ART was initiated at three different time points: (i) early –integrated therapy (214 patients), within 4 weeks of starting TB therapy, (ii) late-integrated therapy (215 patients), within 4 weeks of intensive phase (2 months), (iii) sequential therapy (213 patients), at the end of TB treatment (6 months). The sequential group was discontinued after a pre-planned interim analysis showed that the death rate was 56% lower (hazard ratio: 0.44, 95%CI 21% to 75%; p =0.003) in the integrated arm compared to sequential arm. The trial concluded that initiation of ART during TB therapy provides survival benefit for patients with CD4 cell counts ≤500 cell/uL. The third arm of this study was stopped and then continued randomizing patients as per SAPIT (2011).

Technically the same study as above, SAPIT (2011)[59] compared the early ART (initiating ART within 4 weeks of TB initiation, 214 patients) versus late integrated arms (initiating ART after 4 weeks of the continuation phase, 215 patients).There were only 5.6% and 4.7% of extra-pulmonary TB in the early versus the late ART but this study did not specify the types of HIV-TBM patients. The study found that there were no differences in the incidence rate of AIDS or death, which was 6.9 cases per 100 person-years in the early-integrated group (18 cases) versus 7.8 cases per 100 person-years in the late-integrated group (19 cases) (incidence rate ratio 0.89; 95% CI: 0.44 to 1.79; p = 0.73). Nevertheless, the incidence of IRIS was significantly higher in the early-integrated group compared to the late-integrated group (4.7 times higher in patients with CD4 counts ≤50 cells/uL and 2.2 times higher in patients with CD4 > 50 cells/uL, p=0.01, p=0.02). As a result, more patients had to switch ART because of adverse events in the early-integrated group. Therefore, the authors concluded that early ART should be initiated for patients with CD4 counts ≤50 cells/uL to increase survival. As for patients with CD4 counts >50 cells/uL, ART should be deferred until the start of the continuation phase of TB treatment (2 months) to prevent risk of IRIS and other ART-related adverse events.

CAMELIA[61] (Cambodian Early Versus Late introduction of antiretroviral therapy) was a multicenter, randomized controlled trial conducted in Cambodia from 2006 to 2009. The study enrolled 661 HIV-infected treatment-naive patients with CD4 cell counts ≤ 200 cells/ uL and newly diagnosed smear-positive TB. The patients were randomized to introduce ART at two different time points: early ART

(332 patients), 2 weeks after starting TB therapy and a late ART (329 patients) and 8 weeks after starting TB treatment**.** The median baseline CD4 cell count was 25cells/uL. The early ART group had a significantly higher rate of survival than the late ART group (hazard ratio, 0.62; 95%CI, 0.44 to 0.86, p=0.006). Nevertheless, IRIS was significantly more common in the early ART group (hazard ratio, 2.51, 95% CI, 1.78 to 3.59, p<0.001). The effect of initiating ART early was not significantly different between the two sub-groups of patients (≤ 50 cells/uL versus 51 to 200 cells/ uL).The study concluded that initiating ART 2 weeks after the start of TB treatment significantly increased survival among HIV patients with CD4 count ≤ 200 cells/uL. The results might not be directly generalisable to all forms and severity levels of TB such as the TB-meningitis as there were no cases related to TB-meningitis in this study.

The STRIDE study [71](Strategy study of Immediate versus deferred initiation of ART for HIV-infected persons treated for TB) was an open-label, randomized controlled trial performed in 809 HIV-infected treatment-naive patients with CD4 cell counts ≤ 250 cells/ uL. They were mainly newly diagnosed smear-positive pulmonary TB. This paper did not specify the number of TBM patients. The median baseline CD4 count was 77 cells/uL. The primary combined outcome was the proportion of patients who survived without new AIDS-defining illnesses at 48 weeks. In the early arm (405 patients) ART was initiated 2 weeks after starting TB therapy, and in the late arm (401 patients) ART was initiated between 8 and 12 weeks after starting TB therapy. In line with SAPIT's (2011) finding, the study found that there were no significant differences in the primary outcome between

the early and late arms. There were 26 new AIDS-defining illnesses and 26 deaths in the earlier-ART group and 37 new AIDS-defining illnesses and 27 deaths in the later-ART group, with no significant difference between the groups with respect to the rates of this combined outcome (12.9%of patients having a new AIDS-defining illness or died vs. 16.1%; 95% confidence interval [CI], −1.8 to 8.1; P=0.45, stratified according to the screening CD4+ T-cell count). Tuberculosis-associated IRIS was significantly higher in earlier ART than in later ART (11% vs. 5%, P = 0.002). Nevertheless the rate of new AIDS or death was significantly lower in the early group than in the late ART group in the sub-group of 285 patients with ≤50 cells/uL (15.5% vs. 26.6%; 95% CI: 1.5 to 20.5; p = 0.02). The study complements and extends the findings from preceding randomized trials which concluded that for patients with CD4 cell counts of 50 cells/uL or higher, waiting 8 to 12 weeks after initiating TB treatment did not increase any risk of a new AIDS-defining illness or death and was likely to lead to fewer cases of IRIS.

The TIME study [72] was an open-label, randomized controlled trial performed in Thailand from 2009 to 2011. A total of 156 HIV-naïve patients with the median CD4 count of 43 cells/uL (53% with disseminated or extra-pulmonary TB) were included. Patients were randomized to early ART 4 weeks (79 patients) after starting TB therapy and late ART arm 12 weeks (77 patients) after TB therapy. This study found that there were no significant differences in the primary outcome (one-year all-cause mortality): early ART (8.76 per 100 patient-years) versus late ART (7.25 per 100 patient-years) (Relative risk (RR): 0.845; 95% CI: 0.247 to 2.893), and no significant differences in survival advantage for subgroups of

patients with baseline CD4 counts ≤50 cells/uL and ≤ 100 cells/uL. The authors concluded that early ART was not associated with survival advantages for patients with CD4 counts ≤ 350 cells/uL. There was 1 patient (1.3 %) and 2 patients (2.5%) who had TB-meningitis in the early and late ART group respectively. TIME included approximately 50% of patients who had extra-pulmonary TB disease, making this study different from SAPIT, CAMELIA, and STRIDE, which focused on pulmonary TB only.

TB-HAART [73] was the first and largest randomized, double-blind, placebo-controlled clinical trial of patients with pulmonary tuberculosis and HIV. This trial recruited 1,675 patients with CD4 counts≥220 cells/uL from South Africa, Tanzania, Uganda and Zambia. Early ART (834 patients) initiated after 2 weeks of tuberculosis treatment was compared with late ART (841 patients) started after 6 months of tuberculosis treatment, from 2008 to 2013. The primary outcome was a composite of death, failure of tuberculosis treatment, and recurrence of tuberculosis at 12 months. The study found that there were no significant differences between study groups in the composite outcomes of tuberculosis treatment failure, tuberculosis recurrence, and death over a 24-month follow-up period (RR: 0.91, 95% CI 0.64 to -1.30; p=0·9). Grade 3 or 4 adverse events and IRIS were similar between the study groups (p>0.05). The study suggested that initiation of ART should be delayed until after completion of 6 months of tuberculosis treatment for HIV/TB patients with high CD4 cell counts (≥220 cells/μL).

Summary of HIV/TB randomized controlled trials evidence: This review identified five trial-based studies addressing the optimal time point to initiate ART in HIV-associated with predominantly pulmonary TB. Conflicting results were reported. A randomized trial in Cambodia, CAMELIA[61]contained mainly pulmonary TB, found that that early ART significantly improved survival of HIV-TB co-infected adults with CD4 counts ≤ 200 cells/μTwo trials (SAPIT (2011)[59], STRIDE[71]found no significant differences between early ART versus late ART except in the sub-analysis of patients with CD4 count ≤50 cells/uL, early initiation of ART during tuberculosis treatment provided survival benefits for these patients. On the other hand, the TIME study (2012)included a high proportion of patients who had extra-pulmonary TB disease (50%) and found no significant differences between early ART versus late ART for HIV-TB co-infected patients with CD4 counts ≤ 350 cells/uL. Another randomized trial in Sub-Saharan Africa [73]found no significant differences in survival between early and late ART for patients with CD4 count ≥ 220 cells/uL. These differences in findings were hard to interpret due to the differences in trial designs and the characteristics of patient populations. It seems that the beneficial effects of early ART may not work well if the study population contains higher proportion of extra-pulmonary TB individuals. One

striking factor is that IRIS occurred more frequently in the early ART arm. The findings of these trials might not be applicable to HIV/TB meningitis patients.

2.4 **Clinical background on the optimal time point to initiate ARV in HIV patients with TBM**

The optimal time to initiate ART for pulmonary TB may differ for HIV patients co-infected with TBM because of the more complex management. TBM is the most severe form of TB and these patients are found to be immunosupressed related to advanced HIV infection, so that the beneficial effects of early ART may not work quickly to alter the early TBM-related mortality. Furthermore, early ART may cause a central nervous system (CNS) IRIS that lead to neurological deterioration or immediate death [56].Therefore, early ART might not reduce the risk of death as demonstrated in the pulmonary TB trial based-studies.

Our randomized, double-blind, placebo-controlled trial [74] recruited 253HIV patients with definite, probable, or possible TBM in Vietnam. All patients had a baseline CD4 cell count of ≤200 cells/μL. The health economics analysis of our trial will be presented in chapter 3. The primary outcome was time from randomization to death in the first 9 months of follow-up. The patients were randomized to immediate ART (1 week after diagnosis of TBM, 127 patients), or deferred ART (after two months of TB treatment, 126 patients). Our trial found that immediate ART was not different in terms of 9-month mortality compared with the deferred ART (HR: 1.12; 95%CI, 0.81 to -1.55; P=0 .50) or the time to new AIDS

events or death (HR: 1.16; 95% CI, 0.87 to -1.55; p=0.31). The majority of deaths (45 in the immediate ART group and 40 in the deferred ART group) occurred within the first month of the study. Significantly, more patients in the immediate ART group experienced grade 4 adverse events (102 vs 87, p=0.04). Immediate ART was also associated with a higher frequency of patients with grade 3 and 4 adverse events (109 vs 95, p=0.04) and grade 4 adverse events during the first 2 months (77 vs 59, p=0.03). Potential causes of these events could be paradoxical reactions (in patients not receiving ART), CNS-IRIS, another CNS opportunistic infection or the use of adjunctive corticosteroids (drug toxicities). Our recommendation was to defer the initiation of ART in patient presenting with HIV-associated with TBM because immediate ART did not improve outcome in patients and increased the frequency of grade 4 adverse events.

Based on these trials above, excluding TBM, for TB patients who have CD4 counts less than 50 cells/μL, ART should be started within 2 weeks of starting tuberculosis treatment, and ART should start within 8-12 weeks after starting tuberculosis treatment if the CD4 cell count is higher than 50 cells/μL. In TBM, ART should be deferred until the end of anti-tuberculous induction treatment unless there is some other compelling reason to start earlier, such as health economic costs. Investigating this last point is part of the purpose of this thesis.

2.5 **Health economics evaluations of ART in HIV-infected patients with TB**

In this section, I present a systematic literature review that evaluates the economic costs, the quality of life, and the cost- effectiveness of ART when treating HIV infection complicated by TB infection. The review is organized into 3 sections. First, I review the costs of treating HIV with antiretroviral treatment in Vietnam and the costs of treating TB and HIV co-infection in developing countries. Secondly, I review the literature regarding the cost-effectiveness of early versus delayed ART in HIV infected patients with opportunistic infections. Finally, I review the available data of ART treatment strategies on the health related quality of life of patients co-infected with HIV and TB.

2.5.1 **Systematic literature review of the costs of ART in HIV-infected patients and in patients with TB co-infection in Vietnam and in developing countries**

2.5.1.1 Introduction

Studies in the costs of care for HIV-TBM patients are difficult because TB meningitis is a relatively rare form of tuberculosis. The vast majority of research is focused on pulmonary disease. TB meningitis is the most severe form of TB, with the highest risks of death and long-term sequelae, such as neurological disability, and therefore the costs associated with this disease are likely to be higher than for

other forms of TB. Collecting these costs can be challenging in low and middle income countries where the resources are limited.

Costing study consists of the identification, measurement and valuation of all resources related to an illness, under which all resources consumed by patients are measured using a monetary value[14]. Costing studies are generally used to estimate the cost of a particular disease or event per person. Results of these studies are then used to estimate the cost-effectiveness of specific interventions. Costing studies are also used to estimate the costs for all patients with particular disease or event within a given region or country to provide a measure of the economic burden of a particular disease. When undertaking the cost analysis of an illness, it is essential to determine the consider the following four criteria [50] illustrated in Table 2-1.

Table 2-1: Criteria to be assessed when conducting cost analysis of illness

Criterion	Explanation
Perspective of the costing study	The perspective determines the cost types and includes the societal or health care provider (hospital), and (or) patient's out of pocket costs.
Identifying the main cost items	There are 3 main types of healthcare costs: -The direct medical costs are incurred from the health sector perspective (such as outpatient services, inpatient medication, diagnostics tests) -The direct non-medical costs from patients and their carers (transportation to the facility, special meals , out-of-pocket expenses made by the patients and their carers due to the disease) -The indirect costs are defined as the productivity losses due to illness, which are the income lost associated with work absenteeism due to illness.
Measurement of the costs	The methods of measuring the costs comprise gross costing and micro-costing. Gross costing requires relatively few resources but provides a limited level of detail. An

	example, of gross costing is if 20% of the hospital patient population receives diagnostic tests, 20% of total hospital costs are then assigned to diagnostic tests. In contrast, micro-costing requires a high level of detail. Micro-costing studies collect detailed data on resources utilized and the value of those resources. Multiple data sources can be involved in the micro-costing approach.
Dealing with uncertainty	The parameter uncertainty is assessed using deterministic univariate (changing one parameter) or multivariate sensitivity analysis (changing multiple parameters).

The first part of this systematic review has two objectives. The first is to review the available evidence on HIV treatment costs in Vietnam. The second is to review the published literature estimating the cost of care for HIV-TB co-infection in low and middle-income countries (LMICs).

2.5.1.2 Methods

Search strategy and inclusion criteria: According to CHEERS guidelines [53]**,** I searched PubMed, Social Science research network (SSRN) and SOLO (Oxford University) databases for articles addressing the costs of HIV/AIDS or HIV and TB co-infection in Vietnam or in developing countries published between 2000 and 2014. The search strategy contain terms for both the subject topic area as well as relevant economic terms. Search terms used were, 'tuberculosis', 'TB', anti-TB 'tuberculosis/HIV', 'meningitis/HIV', 'ART', 'HAART', 'early treatment', 'economic analysis', 'costs', 'developing countries', "LMICs', 'Vietnam'. The search strategy was broad so as to avoid missing any relevant studies. Full details of the search strategy and terms are given in the Appendix 2.

Inclusion criteria for considering studies for this systematic review: Peer-review articles, systematic review, and international reports (WHO) assessed the primary

cost of treating HIV, TB, meningitis and co-infected HIV/TB or HIV/meningitis. When determining total costs, resource use had to be derived from studies using patient-level data which could include prospective and retrospective studies and randomized controlled trials (RCTs). Studies where resource use was derived from other studies, modeling or expert opinion were excluded. Prices or unit costs could be derived from any sources, including administrative data, national account data or published studies. Studies reported mean and /or median costs.

Data extraction: Data extraction sheet was used, the composition of which was informed by the data-extraction guidelines for economic evaluations in the Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care Systematic Reviews of Interventions [75]. Titles and abstracts of all identified articles were checked. The full texts of all potential eligible studies and for those studies where relevance were obtained. The following information was extracted from each of the identified studies: author(s), year of publication, study question, patient population and sample size,, intervention, comparator and setting (country where study was based, urban/rural area), study design used to derive resource use; sources and quality of clinical and cost data, time horizon, use of discounting and year of costing, The outcome measure was mean treatment costs per patient For each paper, all cost items reported, such as drugs, hospitalisation, diagnostic tests and productivity loss, were extracted separately and, where relevant, divided into patient-incurred and provider costs. Patient-incurred costs were further divided into direct costs and productivity losses. The limitations of each study were also

identified in order to inform the strengths of the conclusions and future studies. The data were extracted into summary tables according to the pre-defined criteria.

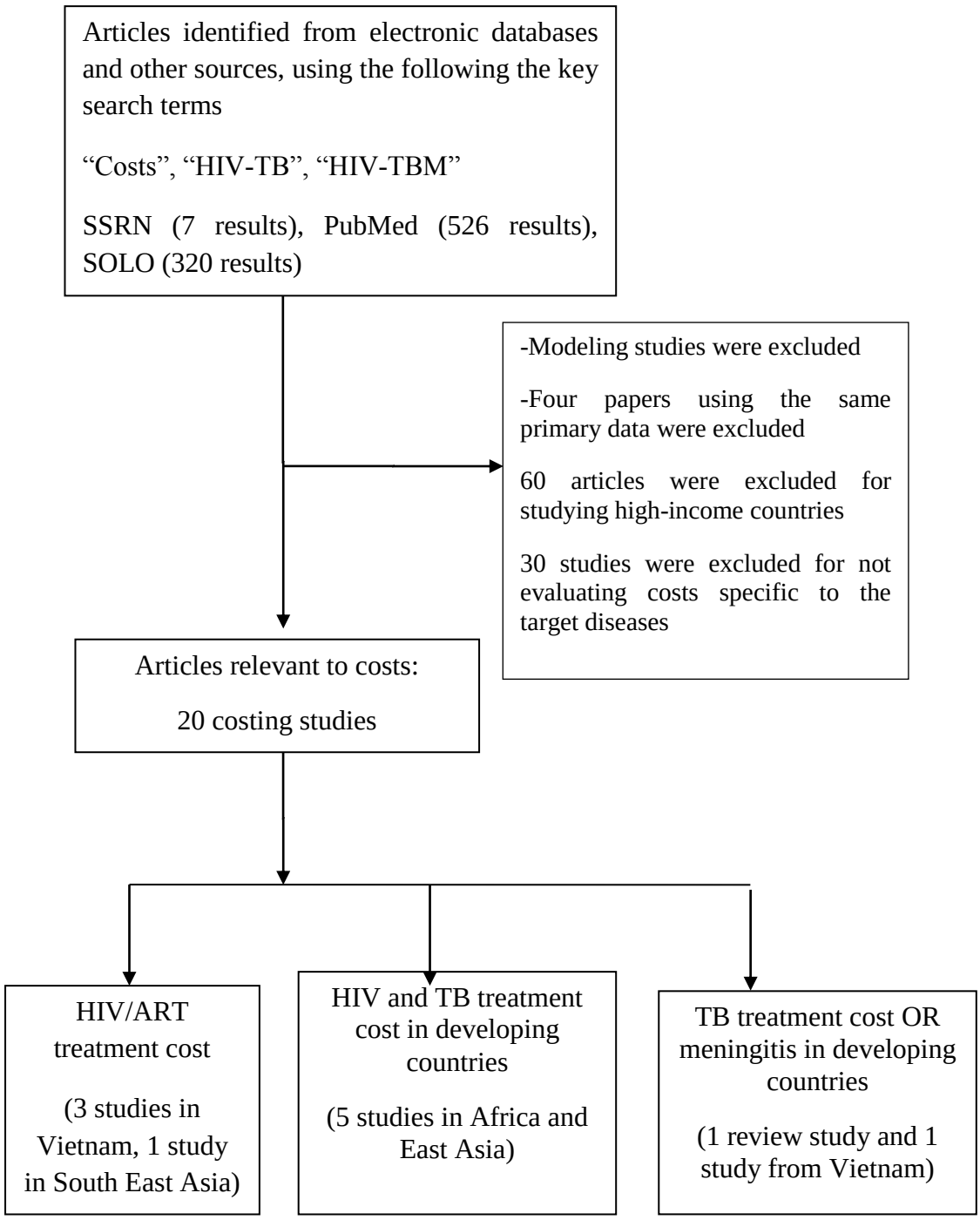
Data analysis:

Firstly, a clear descriptive summary of the included studies was provided. This was done by tabulating details about study type, interventions, population, numbers of participants, patient characteristics, country, perspective, comparison of interventions, and measure of cost. All costs were adjusted to 2013 US dollars (USD) through an initial conversion of study year costs to local currency, followed by an application of the International Monetary Fund's average consumer price indices growth in local currency, and then a conversion between 2013 local currency and 2013 USD through World Bank's average annual exchange rates.

Secondly, a narrative synthesis was undertaken to draw results together. I captured the average (mean and/or median) total costs from each of identified study estimated as the sum of direct medical costs, direct non-medical costs, and indirect costs. These types of costs were summarized for the duration of ART (12 months) or TB treatment (from 6 to 9 months) because these treatment durations are usually expressed in the literature. Study quality assessment: Quality appraisal of studies was drawn from the general health economic evaluations (the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement). These studies were evaluated against the three main criteria of the CHEERS statement: (1) sources used for resource quantities and unit costs clearly described, (2) methods for adjusting unit costs to the reporting year and performing currency conversion

explained, and (3) mean values for main categories of estimated costs reported. These studies were also evaluated against two criteria of CHEER if the productivity losses were included: (1) The methods used for valuing productivity losses explained and justified. (2) Methods of quantifying presenteeism at and absenteesim from paid work as well as productivity losses related to unpaid labour.

Figure 2-2: Flowchart detailing study selection for costing studies



2.5.1.3 Results:

Figure 2-2 details the results of the database search. 853 potentially relevant articles were identified and screened according to their title and abstract. The full texts of 9 articles deemed relevant after screening were retrieved (Figure 2-2). The search identified four costing studies of HIV care in Vietnam, and five costing studies of HIV-TB studies in developing countries. One review study reported the cost of treating TB and one review study on the cost of treating meningitis in low and middle-income countries. However, I found no studies evaluating the cost of care for HIV-TB co infection or meningitis complicated by HIV in Vietnam.

Costing studies of TB in developing countries:

A systematic review of papers conducted by Vassall et al (2015) assessed provider-incurred as well as patient-incurred costs of treating both primary drug-susceptible (DS) [76] in low and middle income countries. The mean provider costs per person were $840 in upper middle-income countries (UMIC), $273 in lower middle-income (LMICs), and $258 in low-income countries (LICs), with the SD as large as the mean provider costs in HICs and larger for LICs. Hospitalisation accounted for 51 % in LMICs ($215) and LICs ($128), but only 12 % in UMICs ($380). This study concluded that costs of TB treatment varied substantially because LICs implemented different ambulatory methods of treatment delivery and various drug regimen prices. This review also observed the highest mean patient costs ($603) in UICs, followed by LICs ($155), and LMICs ($84). Approximately half of patient

costs, the highest proportion, was recorded in the 'other' category, which mainly consisted of non-TB drugs and food while hospitalized, user fees comprised 23%, drugs 9%, and transportation 19 % of total costs. In LMICs, productivity losses was valued from $12 per patient in Indonesia compared with $996 in Vietnam [77]. The methods used to estimate productivity loss vary widely; leading to the productivity losses vary substantially globally,

Costing studies of meningitis in developing countries and in Vietnam:

A systematic review of the literature examined the cost of meningitis care in LMICs for different types of infection (bacteria, viruses, fungi and parasites) [78]. Based on the multiple regression model, these costs ranged from $42 to $9300. The mean treatment cost by income level was $170 for LICs; $790 for LMICs and $2100 for UICs. However, this review did not differentiate the treatment cost attributable to different infection severity of meningitis or estimate the indirect costs.

As for the treatment cost of bacterial meningitis in Vietnam, Phuc Le et al (2014)[79] found that the average cost per patient of meningitis among children < 5 years old was $727 at Bach Mai hospital in Hanoi. This finding was considerably higher than the cost of treating HIV/AIDS per patient per year in Vietnam ($411 Table 2-4) but lower than the cost of treating HIV-coinfected TB ($946 Table 2.7). Direct medical costs accounted more than half of the half of total treatment costs. Direct medical costs (the sum of the costs of resources from outpatient services,

inpatient medication, diagnostic tests, specialized services and medical supplies) were $300 per case of bacterial meningitis.

Summary of costing studies of treating drug-susceptible TB and meningitis:

Table 2-2 showed that the cost of treatment of meningitis in Vietnam was approximately comparable to that of treatment costs of TB in LMIC (meningitis $300 versus TB in LMICs $273). In contrast, the cost of treatment of TB treatment in UMIC was two times higher than the direct medical cost of treating meningitis (TB in UMIC $840). Productivity losses on TB treatment were significantly higher than the meningitis treatment. The differences in costs could be due to the longer treatment duration of TB which normally took about 6 month to 9 months while treatment of acute meningitis might last around 2 months.

Table 2-2: Average (mean) direct medical costs, direct non-medical costs and indirect costs of treating TB or meningitis patients disaggregated by studies The average costs per person per year adjusted to 2013 USD are illustrated here. **(**Data derived from [76,79])

Income group	Hospital stay	Outpatient visits	Drugs	Diagnostic and monitoring tests	Other	Total direct medical costs	SD
DS - TB							
UMIC (n=19) [76]	380	218	107	69	386 **	840 (15)	1105
LMIC (n=10) [76]	215	75	39	48	25 **	273 (10)	212
LIC(n=11) [76]	128	61	49	19	50 **	258 (11)	352
Meningitis							
Children less than 5 years (n =15) in Bach Mai hospital, Vietnam [79]	122	0.89	90	60	27*	300	351

*Medical supplies: syringes, gloves, intravenous catheters, tubes, etc** Other provider costs include start-up costs, treatment supervision, staff salary and training, advocacy, adverse effects, contact tracing, supplies and transportation, or in some papers, where costs were not disaggregated, the total treatment costs to the provider, including supervision, training, supplies and drugs.

Income group	Clinic visits and clinical tests user fees	Drugs	Transport	Other	Total direct non-medical costs	SD	Productivity losses	SD
DS - TB								
UMIC (n=19) [76]	221 (9)	62 (4)	120 (13)	491 (12)*	603 (18)	868	600 (12)	847
LMIC (n=17) [76]	55 (9)	21 (7)	9 (4)	47 (10)*	84 (17)	90	238 (11)	320
LIC(n=19) [76]	49 (13)	38 (5)	45 (10)	96 (16) *	155 (19)	164	248(14)	266
Meningitis								
Children less than 5 years (n =15) in Bach Mai hospital, Vietnam [79]	46		9	101*	156	109	140	46

* Lodging, soap, diapers, etc. **Other patient costs typically include direct medical costs (non-TB drugs, hospitalisation) and direct non-medical costs (food, drink, vitamins, traditional medicine, and accommodation), or in some papers, where costs were not disaggregated, the total costs during pre-diagnosis, diagnosis, intensive treatment and continuation treatment phases

2.5.1.3.1 **Costing studies of ART in HIV-infected patients in Vietnam:**

The four ART costing studies are summarised in Tables 2-3, 2.4 and 2.5 and in Figure 2.3.

Table 2-3: Summary of costing studies for HIV infected patients in Vietnam

Studies	Tran (2013) [80]	Duong (2014) [81]	Nguyen (2014) [82]	Menzies (2014) [83]
Country	Single country	Single country	Single country	Multi-country
Study design	Cross sectional multi-site survey	Retrospective study Patient record forms	Cross sectional multi-site survey and interviews	Patient record forms and interviews
Perspective	Patient and healthcare provider	Healthcare provider	Societal	Healthcare provider
Setting (rural or urban)	Urban central provinces and districts	Urban	Urban	Urban and rural
Inpatient or outpatient	33.8% inpatient 32% outpatient care	Inpatient and outpatient	Outpatient	Outpatient
Sample size	1016 HIV/AIDs patients	1401 HIV/AIDs with OIs patients	315 HIV/AIDs patients	106,906 HIV/AIDS patients
Study population HIV/AIDS stages	343 inpatients 325 outpatients Asymptomatic (12.4%) Symptomatic (50%) and AIDS (37.6%)	305 pre ART, 332 ART year 1, 323 ART year 2 and 122 second line ART and 319 inpatient care	43 pre-treatment 250 first-line regime 22 second-line regime	62,512 ART and 44,394 pre-ART patients
Costing year	2011	2008-2010	2012	2006 to 2007
Unit cost of analysis	-Average cost for an inpatient and an outpatient care -Average annual healthcare costs for an HIVAIDS patient	-Average outpatient cost per patient-year -Average inpatient cost per episode	Average annual cost per patient	Average annual cost per patient
Average cost	$188 (total) $50 (outpatient)	$348 (outpatient)	$611 (outpatient)	$880 (outpatient)

Studies	Tran (2013) [80]		Duong (2014) [81]	Nguyen (2014) [82]	Menzies (2014) [83]
	$461 (inpatient) Excluding ARVs		$235 (inpatient) Including ARVs	Including ARVs	Including ARVs
Adjusted average costs to 2013 USD	$230 (total) $61 (outpatient) $564 (inpatient)		$434 (outpatient) $293 (inpatient)	$687 (outpatient)	$1076 (outpatient)
Direct medical cost (% of total cost)	58% (outpatient)	60% (inpatient)	100% (outpatient and inpatient)	56% (outpatient)	100% (outpatient)
Study limitation	Patients from rural areas and the indirect costs were not included		Patients from rural areas and the indirect costs were not included	Cost of hospitalization were excluded	Cost of hospitalization and TB treatment were excluded
Determinants of the costs	Monthly income, CD4 counts $\leq$ 200 cells/µL and those taken ART over 2 years, from central provinces		Facility types, level of immunodeficiency, donor support	Distance from house to clinic and monthly household income	Duration of ART
Sensitivity analysis	No		Yes, one-way univariate for scenarios of incomplete recording OI drugs, or lower ART year 1 cost	No	No

Table 2-4:Average (mean) direct medical costs, direct non-medical costs and indirect costs of treating HIV/AIDS patients in Vietnam disaggregated by studies The average costs per person per year adjusted to 2013 USD are illustrated here.

Studies	**Direct medical cost**		**Direct non-medical costs**		**Indirect cost****		**Average total cost per person per year**
	Average cost per patient per year	Proportion of the average total costs (%)	Average cost per patient per year	Proportion of the average total costs (%)	Average cost per patient per year	Proportion of the average total costs (%)	
Tran 2013 outpatient (exc.ARV) [80]	138	60%	92	40%	0	0	230
Duong 2014 outpatient (inc.ARV) [81]	434	100%	0	0	0	0	434
Nguyen 2014 outpatient (inc.ARV) [82]	385	56%	151	22%	151	22%	687
Duong 2014 inpatient (exc.ARV) [81]	293	100%	0	0	0	0	293
Average healthcare costs	**312**	**79%**	**61**	**15.5%**	**38**	**5.5%**	**411**

** Income lost from lost work time

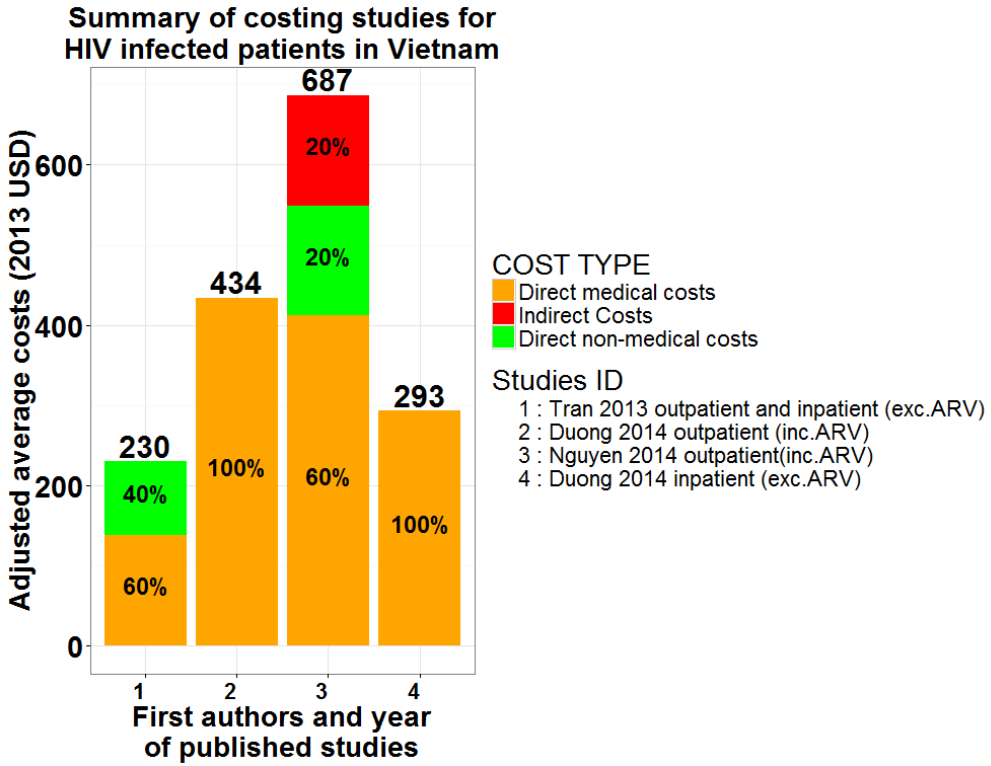


Figure 2-3: Summary of HIV/AIDS costing studies in Vietnam. The average healthcare costs for HIV/AIDS per patient per year are presented across studies with different years of publication. The mean adjusted costs are the costs converted to 2013 US dollars. The colours indicate the 3 main costs: direct medical costs (yellow), indirect costs (red) and direct non-medical costs (green).

Table 2-5: Average healthcare costs (mean) per person per year of treating HIV/AIDS patients in Vietnam according to different cost items and the proportion of the average total costs (%). The average costs per person per year adjusted to 2013 USD are illustrated here.

Studies	**ARV drugs**		**Medication**		**Diagnostic test**		**Others**		**Boarding and lodging**		**Transportation**		**Income lost**		**Mean total cost per person per year**
	Mean cost per patient per year	%	Mean cost per patient per year	%	Mean cost per patient per year	%	Mean cost per patient per year	%	Mean cost per patient per year	%	Mean cost per patient per year	%	Mean cost per patient per year	%	
Duong 2014 outpatient	161	37%	87	20%	65	15%	117	27%[1]	0	0	0	0	0	0	434
Nguyen 2014 outpatient	110	16%	55	8%	117	17%	117	17%[2]	41	6%	96	14%	151	22%	687
Duong 2014 inpatient	0	0	103	35%	59	20%	132	45%[3]	0	0	0	0	0	0	293
Average outpatient costs	**135**	**27%**	**71**	**14%**	**91**	**16%**	**117**	**22%**	**20**	**3%**	**48**	**7%**	**75**	**11 %**	**560**
Average inpatient costs			**103**	**35%**	**59**	**20%**	**132**	**45%**							**293**

[1] Others = Labor (19%) + Overhead (8%)
[2] Others = Healthcare staff (11%) + Amortization (1%) + Administration (1%) + Medical supplies (3%) [3] Others = Labor (29%) + Overhead (16%)

Duong and colleagues [81] examined the direct medical costs of ART, but did not assess the patient's financial burden in terms of travelling expenses or loss of work time. The study was conducted in 2009 and reported inpatient costs and outpatient costs for 1,401 HIV/AIDS adults (305 pre-ART, 332 ART year 1 and 323 ART year 2 and 5 ART second-line) with opportunistic infections attending 21 sentinel facilities in Vietnam. The main components of the total costs were diagnostic tests, ARV drugs (stavudine (d4T) + lamivudine (3TC) +nevirapine/ efavirenz), OI drugs, labor, and overhead costs. This study did not state clearly the type of opportunistic infections involved. The average outpatient care cost (including ARV costs) per patient- year was estimated at $348 (median cost $316, range: $185 to $465) (2010 USD) or $434 (median cost $395) (2013 USD). The average inpatient care cost per episode were $293 (2013 USD)(median cost $202) for the first year of ART. However these inpatient costs did not take account the costs of ARV drugs. Once ART was initiated, the largest cost component was ARV drugs, which accounted for 37% of the total costs per patient-year for ART year 1 ($262 at government sites, $161 at President's Emergency Plan for AIDS Relief (PEPFAR) and Global Fund-supported sites).

Menzies [83] undertook a cost analysis conducted at 43 PEPFAR supported outpatient clinics in Botswana, Ethiopia, Nigeria, Uganda, and Vietnam. The study population included 65,512 ART and 44,394 pre-ART patients. This study was conducted in 2006 and found that median annual outpatient care costs were $880 (range: 600-999) (2009USD) or $1076 (2013 USD) for ART patients. This study

did not report the mean cost, hindering its comparability with other studies. These median outpatient healthcare costs were higher than those estimated in Duong‘s study [81] which yielded $395 per year. Comparison of the costing study results was difficult because of the methodological differences. The higher outpatient costs may have been driven by higher prices of ARV drugs ($699 compared to $161 at sites in Duong’s study. This study would have used the American drug. Furthermore this study also included more comprehensive program costs such as training, supervision and overhead costs into the direct medical costs.

Tran and colleagues [84]reported out-of-pocket (OOP) health payments of 1016 HIV/AIDS patients (12.4% asymptomatic, 50% symptomatic, 37.6% AIDs).This study did not identify patients that had opportunistic infections. Tran found that HIV/AIDs patients paid on average (mean) $188 (95% CI: 148 to 229) (2012 USD) or $230 (2013 USD) per year for their healthcare. This cost covered two types of costs: (i) direct medical costs (non-ARV medications, lab tests, hospital fees and others) and (ii) direct non-medical costs (transportation, boarding and lodging). Therefore, the total costs included the sum of direct medical costs and direct non-medical costs. This cost covered 60% of the direct medical costs ($138, 2013 USD) excluding ARV expenditures, on the grounds that ART was currently provided free of charge in Vietnam during this time. Non-ARV medication accounted for the largest part of the direct medical costs (30%). The direct non-medical costs (such as transportation, boarding and lodging) accounted for 40% of the total costs at $92 per person per year. This study found that more than one-third of HIV-affected households experienced catastrophic health expenditure. Health expenditure was

viewed as catastrophic whenever it is greater than or equal to 40% of a household's non-subsistence income, income available after basic needs have been met[85].

Nguyen and colleagues [82]analyzed the outpatient costs of 315 HIV/AIDS patients in a central outpatient clinic in Bach Mai hospital in Hanoi, Vietnam during the year 2012. This study specifically focused on the direct medical costs (including ARV) and non-medical costs (other medications, travel costs, meals, accommodation), and opportunity costs in the form of lost working days by patients and caregivers. The mean total cost of outpatient care was $687 (2013 USD), with 56% of the burden falling on direct health care funding sources ($385) and 44% on the patients' families ($302). The direct medical costs ($385) in this study were comparable with the outpatient ART costs in Duong's study which was estimated at $434 per year[81]. Including the non-medical costs and income loss doubled the treatment costs from $434 to $687 per person per year in Vietnam.

Summary and interpretation of costing studies of ART in HIV-infected patients in Vietnam

Taking into account all the costs, HIV-patients (with opportunistic infections) on antiretroviral therapy in Vietnam were likely to incur the mean total costs between $230 and $687 per year, with an unweighted average of $411 per person per year for their inpatient and outpatient care (including ARV drugs, direct and indirect costs). On average, 79% of the total cost was due to direct medical costs, 15% to direct non-medical costs, and 6% to income loss (Table 2-5, Figure 2-3).ARVs accounted for 33% of the direct medical costs, following by the diagnostic tests (22%), the non-ARV drugs (17%) and other medical services (28%). Travelling

costs accounted for 70% of the direct non-medical costs, following by the boarding and lodging (30%) (Table 2-4).

International reports

The ARV costs in this systematic review were in line with the findings from PEPFAR report [86] and WHO Global price reporting mechanism on transaction prices for antiretroviral medicines report [87] regarding the average cost per person receiving ART in programs supported by PEPFAR . In 2013, PEPFAR released a study showing that treatment costs at their sites had declined from over $1,1000 per person per year to about $338 during the period 2004 to 2011[86]. The cost of the fixed-dose combination of the WHO-recommended first-line regimen of TDF + FTC + EFV was US$ 186 per person per year in 2012; these reports reflect the significant drop in ARV prices that has occurred from 2001 to 2012.

2.5.1.3.2 **Treatment costs for patients co-infected with TB and HIV in low and middle-income countries**

Very few studies were identified that addressed the costs of treating HIV and TB co-infection in low/middle income countries. Those identified usually measured the costs incurred by TB patients or HIV patients alone. This section presents results from five studies that mainly estimated the patient costs of TB-HIV care in terms of direct and indirect costs in African and South East Asian countries. The five studies are summarized in Table 2-6 and Table 2-7 and Table 2- 8 and Figure 2-4. This review found that there were no international reports that evaluated the co-treatment of TB and HIV.

Table 2-6**:** Summary of costing studies for patients co-infected HIV and TB in developing countries

First author, year, reference	**Sony (2006)** [88]	**Sadoh (2007)** [89]	**Vassal (2010)** [90]	**Mauch (2013)**[7] [77]	**Mauch (2013)** [77]	**Mauch (2013)** [77]	**Ukwaja (2011)** [91]
Country	Sudan	Nigeria	Ethiopia	Ghana	Vietnam	Dominican Republic	Nigeria
Sample size	73	14	41	135	258	150	452 newly TB patients
Population	HIV-TB	HIV-TB	HIV-TB	65% smear-position TB 26% smear-negative TB 9 % EPTB 22% HIV-position 67% HIV-negative 11% not know	58% smear-position TB 23% smear-negative TB 19 % EPTB 4% HIV-position 67% HIV-negative 39% not know	69% smear-position TB 11% smear-negative TB 20 % EPTB 11% HIV-position 66% HIV-negative 23% not know	29% HIV positive 71% HIV negative 80.1% smear positive TB 19.1% smear negative TB
Duration of TB treatment	6 to 12 months	6 months	8 months	6 months of TB treatment + 6 weeks pre-diagnosis	8 months of TB treatment + unreported pre-diagnosis	6 months of TB treatment + 7 weeks pre-diagnosis	6 months of TB treatment plus 8 weeks of pre-treatment/diagnosis for TB
Costing year	2000	2005	2005	2005	2005	2005	2011
Study design	A prospective cohort	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional study
Perspective	Healthcare provider	Societal	Societal	Societal	Societal	Societal	Societal
Inpatient/outpatient	Inpatient and outpatient	Outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Unclear
Average cost per patient (currency as	105	300	533	538	1021	1268	704

First author, year, reference	Sony (2006) [88]	Sadoh (2007) [89]	Vassal (2010) [90]	Mauch (2013)[7] [77]	Mauch (2013) [77]	Mauch (2013) [77]	Ukwaja (2011) [91]
in the study)							
Adjusted average cost (2013 USD)	297	547	1031	624	1789	1487	845
Cost included	Direct medical costs (100%)[1]	Direct medical costs (92%)[2] Direct non-medical (8%)[3]	Direct medical costs (58%)[4] Direct-non medical costs (11%) [5] Indirect costs (31%)[6]	Pre-diagnosis direct (6%) Pre-diangosis indirect (70%) Post-diagnosis direct medical cost (15%) Post-diagnosis indirect (4%)	Pre-diagnosis direct (9%) Pre-diangosis indirect (81%) Post-diagnosis direct (7%) Post-diagnosis indirect (3%)	Pre-diagnosis direct (3%) Pre-diangosis indirect (82%) Post-diagnosis direct (10%) Post-diagnosis indirect (5%)	Pre-diagnosis direct (9%) Pre-diangosis indirect (72%) Post-diagnosis direct (6%) Post-diagnosis indirect (13%)
Limitation	No inclusion of HIV-TB at severe state	Recall and reporting bias	Inclusion of only urban population	No statistical comparisons between countries No TB-meningitis assessment			Recall and reporting bias No TB-meningitis assessment
Sensitivity analysis	No	No	No	No			Yes, one-way for drug prices (+/- 25%)

[1]Direct medical cost =Diagnosis (46%) + Drugs excluding ARV (15%) + Side effects (0.09%) + Intercurrent symptoms (4%) + Hospitalization (35%)

[2]Direct medicalcosts= subsidized HIV treatment cost (of drugs including consumables and cost of laboratory tests such as CD4 count and viral load tests), plus charges for the consultation and the costs of TB drugs and routine investigations (chest radiograph, Mantoux tests, full blood count..).

[3]The direct non-medical = patients and their care giver's transport cost on clinic visits (to and from the hospital).

[4] Direct medical cost = TB treatment smear-position for in-patients (61%) + INH prophylaxis for out-patients (8%) + Cotrimoxazole prophylaxis for out-patients (2%) + Voluntary counselling and testing (1%) + Antiretroviral treatment first year of treatment (26%) + Treatment for OI requiring 1 out-patients visit (2%)

[5] Direct non-medical cost = transport cost + caregiver cost

[6] Income lost = the loss of household income from production and employment

[7] In Mauch 2013 study, direct costs during TB diagnosis included administrative charges, non-TB tests, x-rays, non-TB drugs, transport costs to and from health facilities, and associated food & accommodation costs. Direct costs during treatment covered hospitalization costs, and food and costs arising from health visits. Indirect costs included income lost during pre-diagnosis and income lost from hospitalization and health visits during treatment.

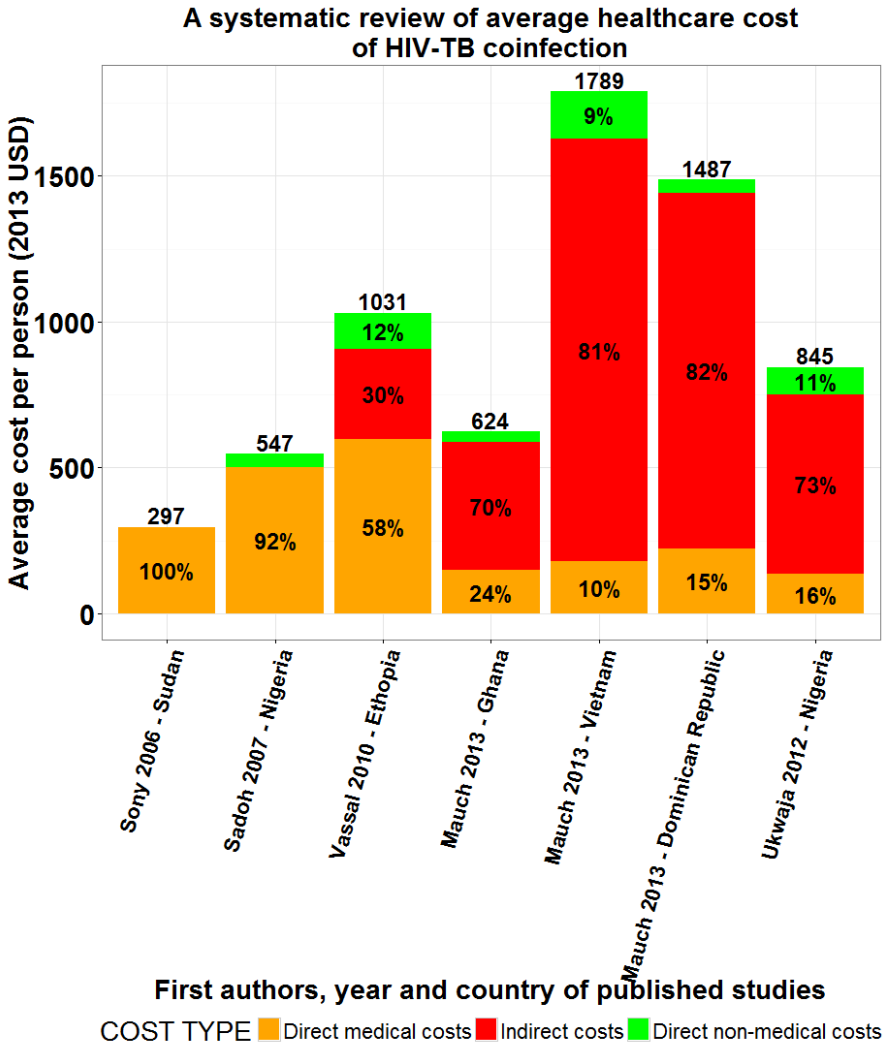


Figure 2-4: Systematic review of HIV/TB costing studies. The average healthcare costs for HIV-TB per patient per year are presented across studies with different years of publication. The mean adjusted costs are the costs converted to 2013 US dollars. The colours indicate the 3 main costs: direct medical costs (yellow), indirect costs (red) and direct non-medical costs (green).

Table 2-7: Summary of average (mean) direct medical costs, direct non-medical costs, and indirect costs of treating HIV/AIDS and TB patients in developing countries. Average costs per patient per year are adjusted to 2013.

Authors, Year, Reference	Countries	Direct medical cost		Direct non-medical		Indirect costs		Total
		Average cost per patient per year	Proportion of the average total costs (%)	Average cost per patient per year	Proportion of the average total costs (%)	Average cost per patient per year	Proportion of the average total costs (%)	Average cost per patient per year
Sony 2006 [88]	Sudan	297	100%	0	0	0	0	297
Sadoh 2007 [89]	Nigeria	503	92%	43.76	8%	0	0	547
Vassal 2010 [90]	Ethiopia	598	58%	124	12%	309	30%	1031
Mauch 2013 [77]	Ghana	150	24%	37	6%	437	70%	624
Mauch 2013 [77]	Vietnam	179	10%	161	9%	1449	81%	1789
Mauch 2013 [77]	Dominican Republic	223	15%	45	3%	1219	82%	1487
Ukwaja 2013[92]	Nigeria	135	16%	93	11%	617	73%	845
Average total costs		**298**	**45%**	**72**	**7%**	**576**	**49%**	**946**

Table 2-8: Average healthcare costs (mean) per person per year of treating HIV/AIDS and TB patients in LMICs according to different cost items and the proportion of the average total costs (%). The average costs per person per year adjusted to 2013 USD are illustrated here.

Studies	Countries Sample size and patient characteristics	ARV drugs		Medication		Diagnostic test		Outpatient consultation		Hospitalisation		Boarding and lodging		Transportation		Income lost		Mean total cost per person per year
		Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	
Sony 2006 [88]	Sudan 1724 HIV-negative TB[a]			137	66	52	25			18	9							207
Sony 2006 [88]	Sudan 73 HIV-positive TB[a]			138	46	55	18.5			103	35							297
Sadoh 2007 [89] [b]	Nigeria 96 HIV patients	294	32													610	68	904
Sadoh 2007 [89]	Nigeria 8 TB patients	324	21													1,206	79	1,530
Sadoh 2007 [89]	Nigeria 24 HIV + TB patients	504	32													1,116	68	1,620

Studies	Countries Sample size and patient characteristics	ARV drugs		Medication		Diagnostic test		Outpatient consultation		Hospitalisation		Boarding and lodging		Transportation		Income lost		Mean total cost per person per year
		Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	
Vassal 2010 [90]	Ethiopia 52 ART patients first year of treatment			126	45							2	0.7	17	6	134	48	279
Vassal 2010 [90]	Ethiopia 91 TB treatment outpatients			134	31							27	6	124	29	151	35	435
Vassal 2010 [90]	Ethiopia 41 TB treatment inpatients			435	69							39	6	23	4	135	21	633
Vassal 2010 [90]	Ethiopia 41 HIV- TB inpatients			608	59							41	4	51	5	330	32	1031
Mauch 2013 [77]	Ghana 135 TB patients			131	21	37	6									456	73	624
Mauch 2013 [77]	Vietnam 258 TB patients	178		10		161	9									1449	81	1789
Mauch 2013 [77]	Dominican Republic 150 TB patients	149		10		45	3									1294	87	1487

Studies	Countries Sample size and patient characteristics	ARV drugs		Medication		Diagnostic test		Outpatient consultation		Hospitalisation		Boarding and lodging		Transportation		Income lost		Mean total cost per person per year
		Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	Mean cost	%	
Ukwaja 2013 [92]	Nigeria 52 newly TB patients	59		7		84.5	10					101		12		599	71	845
Naido o et al 2015 [93] [C]	South Africa 214 Arm 1 receiving ART within 4 weeks	411	32	2.1	0.2	386	30	186	14	301	23							1,286
Naidoo et al 2015 [93]	South Africa 215 Arm 2 receiving ART after 2 months	313	25	3.1	0.2	416	34	171	14	334	27							1,237
Naidoo et al 2015 [93] Arm 3	South Africa 213 Arm 3 receiving ART after 6 months	84	7.6	3.5	0.1	358	32	107	15	554	46							1,106

[a]Sony et al (2006) Capital, training, and administrative costs related to improving the services were not estimated . Medications include the drugs = $15.7 for HIV negative patients and $16.1 for HIV positive patients, and the cost of drugs taken for side effects for 165 HIV negative and 6 HIV-positive of the TB patients = $1.6 for HIV negative patients and $1 for HIV positive patients and the cost of intercurrent symptoms = $5.64 for HIV –negative patients and $6.83 for HIV positive patients. Average treatment days 42.4 for HIV-negative patients and 52.3 days for HIV positive patients. The total sample size was 1724 TB patients and 73 HIV-TB patients. The number of hospitalized patients were 80 for TB arm and 14 for HIV-T B patients. Total costs for hospitalization were $11281 for TB patients and 2671 for HIV-TB patients

Sadoh et al (2007) did not aggregate the cost of treatment in the study. It is known that the cost of treatment consisted of subsidized HIV treatment cost (of drugs including consumables and cost of laboratory tests such as routine laboratory tests such as CD4 count and viral load determination) plus charges for the consultation, the cost of purchasing anti-TB drugs syringes and needles and the cost of investigations for TB (chest radiograph, Mantoux tests, full blood count, erythrocyte sedimentation rate, etc). Income lost = Income lost for treatment and transportation

[C]: Naidoo et al (2015): The cost of voluntary counselling and testing, screening and baseline consultations, TB diagnostics, TB treatment, capital costs, fixed costs and overhead costs were excluded. Medication use: ART doses were specified, and for other medications standard doses were assumed. Provincial ART tender prices (valid to December 2010) were used to cost ART. This include the cost of CD4+ count, viral load testing, X-rays and all other laboratory tests. It includes staff cost, the price paid for investigations and consumables cost. The total sample size was 642 HIV-TB patients

A prospective cohort study from Sudan [88] compared the costs of management of TB between those who were HIV positive (73 individuals) and those who were HIV-negative (1797 individuals) based on the hypothesis that HIV positive TB patients were likely to incur higher costs of care than TB patients without HIV infection. This study found the average direct medical costs per HIV-TB patient treated to be $297 (2013 USD conversion rate), which was significantly higher than for HIV-negative TB patients ($105.08 versus $73.92, p=0.003,Student's t-test). This cost difference was mainly due to greater costs of hospitalization for HIV-positive patients than for HIV-negative patients. HIV-positive patients had longer mean duration of hospitalization (52 days vs 42 days) and higher proportion of hospitalized patients (19.2% vs 4.6%, $p<0.001$). However, in this study costs of diagnostic tests for management of adverse reactions and for intercurrent symptoms and opportunistic infections were not significantly different ($p>0.05$) between the two groups because very few patients were severely immune suppressed (and therefore they were less likely to develop additional opportunistic infections). They tolerated the TB drugs well, leading to low complications from treatment.

A study from Nigeria [89] evaluated the cost burden to families of 96 HIV/AIDS individuals, 8 TB and 24 AIDS/TB co-infected individuals, taking into account income lost for transport and treatment in Benin from 2005 to 2006. The cost of treatment consisted of the subsidized cost of HIV treatment. This covered the

the subsidized monthly course of ART as well as cost of laboratory test (CD4 count and viral load determination) was $7.87 (2005 USD). The treatment cost included the costs of TB drugs, the hospital charges for consultations, and the cost of investigations for TB (chest radiograph, Mantoux tests, full blood count, erythrocyte sedimentation rate). The study found that mean monthly treatment cost was significantly higher for families in the co-infected group than for families in

the HIV-only or TB only groups (P<0.001) based on the Tukey-Kramer multiple comparison tests (HIV only: \$26.87 ± \$7.72, TB only: \$29.86 ± \$4.58, HIV/TB co-infection: \$46.14 ± \$6.19). The mean percentage of total monthly income spent on transportation and treatment was significantly higher in the HIV/TB group compared to the TB only and HIV only groups (p<0.0001). If the treatment and transport costs and the income lost for were included, the estimated mean total cost burden to the families over the six-month observation period was approximately \$496 for HIV only, \$1,120 for TB only and 1,621 (2013 USD) for the HIV-TB group. This study found that 42.86% of families in the HIV/TB cohort spent more than their monthly income on treatment and were in extreme difficulty.

Vassal and colleagues [90] measured the patient costs of tuberculosis and HIV collaborative services from hospital-based pilot sites in Ethiopia in 2005. This study recruited 184 patients who had been diagnosed with and were receiving treatment for either TB, HIV-related illnesses or both (52 TB patients with unknown HIV status, 41 TB + HIV patients, and 91 HIV patients).In contrast to the previous studies, the cost items included direct costs, indirect costs and carer's costs. These costs also covered the costs of outpatient (including ARV and TB drugs) and inpatient care, and costs of opportunistic infections (OI). The treatment of most OIs required between 1 and 4 out-patients visits. The study found that the mean total costs were \$1031, \$1061, \$1105, and \$1165 (2013 USD) during the treatment period for one to four out-patient visits for OIs. Direct medical costs were the most significant component of the total cost (58%) following by indirect costs (30%), transport costs (6%), and carer's cost (6%). One limitation of this study is its generalizability to other settings, as the study population primarily consisted of those living near the hospital in an urban setting.

A study by Mauch and colleagues [77]recruited TB patients in Ghana (135 patients), Viet Nam (258 patients) and the Dominican Republic (150 patients).Across the three countries, TB diagnostics (sputum smear microscopy) and treatment (first-line TB drugs) were provided free of charge, while X-rays and hospitalization were charged. Of all patients in the study, HIV-TB co-infection accounted for 22% of patients in Ghana, 4% in Vietnam, and 11% in the Dominican Republic. Extra-pulmonary TB (EPTB) accounted for 9% of patients in Ghana, 19% in Vietnam and 20% in the Dominican Republic. In all countries nearly a third of all patients were hospitalised at some point for TB. The study assessed the direct and indirect costs of tuberculosis diagnosis and treatment for patients. The costs covered the pre-treatment period (about 7 to 8 weeks) for each country, and the treatment periods, which were 6 months for Ghana and Dominican Republic and 8 months for Vietnam. The study found that average (mean) total healthcare costs were in the range of $624 (Ghana), $1,789 (Vietnam), and $1,487 (Dominican Republic) (2013 USD). Measures of precision around these costs were not provided. Vietnam incurred higher costs than the other two countries because of longer treatment durations of tuberculosis and the country were less involved with the private sector in public-private projects focusing on reducing travel, accommodation, and hospitalization costs for TB patients and their caregivers. In all three countries, during treatment, hospitalization and additional food items were the most significant part of direct treatment cost. In Vietnam, TB-patients incurred a mean additional cost of $37 if also being treated for other diseases. In the Dominican Republic, HIV-positive TB patients had more direct (+$2) and indirect (+$600) costs than HIV-negative patients due to more health facility visits.

Ukwaja and colleagues [92]reported a cross-sectional study in Nigeria recruited 452 newly diagnosed pulmonary TB patients. Among them, 29% of these patients were HIV positive. In Southeast Nigeria, the public sector provided free-of-charge

TB services (consultations, diagnostic tests, drugs and hospitalization). The mean total patient and caretaker's cost (direct and indirect) was $845 (2013 USD). Direct treatment costs were mainly attributable to transportation during drug collection/follow-up visits (70% of the direct treatment cost); food (13% of the direct treatment cost); and hospitalisation and user fees (17% of the direct treatment cost). This study found that compared with HIV-negative patients, HIV-positive patients incurred 43% higher direct costs during the pre- treatment period ($53 vs $76, $p<0.001$) and 11% higher direct treatment costs associated with receiving ART drugs, but this difference just failed to reach conventional levels of statistical significance ($39 vs $35, $p=0.06$). The study concluded that patient costs for TB care were potentially catastrophic even where services were provided free-of-charge.

Summary and interpretation of treatment costs for patients co-infected with TB and HIV in low and middle income countries

HIV-patients co-infected with TB on antiretroviral therapy were likely to incur mean total costs ranging from $297 to $1789, with an unweighted average of $946 per person per year (direct and indirect costs and carer's costs). On average, 45% of the total cost was the attributable to direct medical costs, 7% to direct non-medical costs, and 49% to income loss (Table 2-6, Table 2.7 and 2.8).The "hospitalization" costs and "income lost for treatment" remained major components of total treatment cost (82% of total treatment costs) for HIV-TB diseases. This review found that the high mean cost of managing TB may push a quarter of people living below the poverty line.

2.5.1.3.3 **Discussion of costing studies of ART in Vietnamese patients**

There are very few studies on HIV treatment and care costs in Vietnam. The country has HIV prevalence similar to that of much of Europe (~0.5% of general

population aged 15 to 60), although it is concentrated in the large conurbations and the large population means significant numbers are infected. Our systematic review estimated that HIV/AIDS infected patients in Vietnam were likely to incur an average of $230 to $687 per year (Table 2-4). Although ARVs were free of charge in Vietnam, the review found that HIV/AIDS patients still had considerable out of pocket expenses for diagnostic tests, non-ARV medication and transport costs that were estimated at an average of $119 per patient per year (Table 2-3 and Table 2-4). The productivity losses were estimated at an average of $75 per patient per year. These costs give an alarming since they exceed the basic health expenditure per capita in Vietnam, estimated at $142 by the World Bank [4]

Of note, the external funds for Vietnam HIV care are anticipated to decline sharply, with the imminent end of the PEPFAR programme. ART may no longer be free, although there are plans for free health insurance for the poorest in society. If the cost of ARV drugs were included, the direct medical costs per patient would increase to $434 per year [81]

The funding for HIV control in Vietnam in 2014 was estimated at $100 million recorded by the USAIDS in 2014[94]with the Vietnamese Government contributing for only 20% and the donors accounted for the remaining portion. Given the current resource allocation, Vietnam cannot sufficiently cover the full cost of ART across the country if international funding is withdrawn- the country is heavily donor dependent. How could such a funding gap be financed? Some have suggested [82,95,96] that the extra funding should be raised through both engaging the private sector via mandatory enrolment in and expanding the use of social health insurance. De-centralising HIV/AIDS-related services to the district level could help to reduce travel costs and loss of income for patients during clinic visits. Government policy should consider subsidising patients' costs in certain circumstances.

In fact, the Department of HIV/AIDS in Vietnam has recently announced that from 01 January 2017 antiretroviral drugs will no longer be free and patients will need to have social health insurance (SHI) to obtain free at the point of use ARV medication. Each person must pay $28 per year to purchase health insurance and will then receive an average of approximately$500 of care per year covering the cost of ARVs and other HIV-associated diagnostics. The cost of SHI will be subsidized by general taxation and it is planned that it will provide cover to 70% of the general population and 53.3% of the HIV/AIDS population[82] . However, at present I am not aware of any other strategies set in place to reduce the high patient non-medical costs or productivity losses. It is anticipated that scaling up free-of-charge ART services, decentralisation and integration of HIV/AIDS-related services might also help to reduce the patient costs of HIV care and treatment in Vietnam.

This review aimed to provide an estimation of HIV/AIDS treatment costs reflecting the current standard practice in Vietnam. However, as seen, few hard data exist and thus the limited findings of this review should be interpreted with caution. Using the CHEERS [97] costing guideline, I identified several key methodological issues that suggest further standardization to develop a set of costs that can be used globally. Three studies considered only outpatient costs, and two studies considered both outpatient and inpatient costs, hindering the ability to observe cost drivers and analyse trends such as ARV drug costs over time. The majority of the studies reported the direct medical costs but only one study reported the income lost associated with HIV treatment. In addition, the studies offered few insight to inpatient treatment, or the treatment of more severe opportunistic infections. Therefore, the results may not accurately reflect how financially significant different stages of HIV disease affect household budgets. Costs in these studies

were not reported using the standardized ingredients approach that should show clearly how many resources were used during treatment as well as the unit prices. Moreover, the studies in this review reported varying metrics to describe costs, including the median, mean, cost per patient-year, and cost per episode. Moreover, only one study conducted a sensitivity analysis (although the data collection was from the survey, which was subject to recall bias (Table 2-6).

2.5.1.3.4 **Costing treatment of HIV/AIDS and TB co-infected patients in LMICs**

There are very few studies reporting the increment in resource consumption resulting from the additional burden of HIV on TB:

Health services costs: Previous studies have looked at the healthcare costs of diagnosis and treatment of TB patients according to their HIV status. One study in Sudan compared the cost of treating 73 HIV-positive and 1724 HIV- negative TB patients [88]. This study demonstrated that during the period of the study, managing HIV-positive TB cases was more costly than managing HIV-negative cases. This difference was largely due to a greater use of inpatient service among the co-infected persons [88] leading to higher cost of hospitalization among these patients [98] and [89].

This study in Sudan [88] also found that the cost of anti-tuberculosis drugs were slightly higher than for HIV-positive patients than HIV-negative patients except those treated with category III who died, failed or defaulted ($16.07 in HIV-positive patients versus $15.72 in HIV-negative patients for all cases) but the differences in costs were not statistically significant.

Sudan study [88] also found no differences between HIV-positive and HIV-negative TB patients in the numbers or in the cost of the diagnostic investigations related to TB. These findings may be true in other developing countries where the

HIV epidemic was in an early phase because at the beginning of the HIV/AIDS epidemic tuberculosis patients with HIV infection was likely to tolerate anti-tuberculosis drugs well. This observation is in contrast to what is generally assumed and requires further investigations. Studies conducted in Africa showed that HIV positive TB patients consumed more services, a greater number of sputum smears and cultures for their diagnosis than HIV-negative TB patients [99,100]. The reasons for additional expenses in treating HIV-positive TB patients could be due to the increased adverse reactions, or recurrent episodes of tuberculosis [101] or HIV-related opportunistic infections [102]. More examinations other than those for TB were incurred among HIV-positive TB patients (urine and stool examination) [88]. This may be explained by complications occurring among HIV-positive TB cases in the African setting, e.g. persistent diarrhea [103].

Patient costs: One study have assessed the income lost on treatment and transport [104] at the household level in Nigeria from 2005 to 2006 for 128 participants (96 HIV only, 8 TB only and 24 HIV co-infected TB children and affected parents). The HIV-TB patients spent significantly higher income on transportation to go the clinic visits and treatment (8.05 +/- 8.68% in HIV-TB compared to the TB only (3.92 ± 4.20%) and HIV only (2.46 + 2.15%), $P<0.01$).

Overall, it can be concluded that the treatment of TB and HIV involved modest increases in several cost categories such as the average costs of diagnosis, laboratory examination, but large increases in costs of hospitalization and managing drug reactions during treatment as compared to treating HIV or TB alone. The main reason could be attributable to need for investigation of apparent drug adverse reactions that was arised from taking two drugs at the same time.

Why were many studies on economics of HIV-co-infected TB ignored? There has been substantial research on direct costs incurred by TB or HIV in LMICs. However, evidence on the cost of TB and HIV co-infection is scarce. It is unclear why the economics of co-infection are ignored in economic evaluations so often. The exclusion of co-infection in economic evaluations could be due to the lack of guidance and standardization of measurement and valuation for health-related co-morbidities [88]. The validated questionnaires for measuring cost of co-infection are scarce and not systematically applied [105]. Second, it could be due to the lack of budget for economic evaluations in this field [106]. Third, the mode of delivery and setting of treating two diseases was complex, and therefore hindered the collection of resource use and unit costs. [100] Fourth, the lack of rigorously routine collection of country-specific cost data for co-infected disease [107] [108]. Inadequate data collection was considered as a limitation of conducting the economics HIV-co-infected TB. Fifth, recent global research did not pay great attention to co-infected disease and normally they were incorporated in the research for the general poverty impact of TB alone or HIV alone [103].

The HIV and TBM trial utilized three studies by Duong (2015) [109] Tran (2013) [110] and Mauch [77] that were identified from the Vietnamese systematic review of economic evaluations by My et al (2014) [1] . These studies provided the prevailing costs of ART and TB treatment at a hospital-level in Vietnam. A simple average was taken for different treatment options for HIV and TB infections and given equal weight [106] to estimate the standardized hospital unit cost/prices used with primary data from these studies to assist providing more up to date estimate of ARV drug cost in 2013 . This new drug prices were used in the sensitivity analysis in Chapter 3 to verify that the cost ARV drug decreased over time in Vietnam during the period from 2007 to 2013.

Mean costs per patient: My review found very few studies evaluating treatment and care costs of HIV-TB co-infected patients. In low and middle-income countries (Sudan, Nigeria, Ethiopia, Ghana, Vietnam, Dominican Republic and Nigeria, the total treatment cost per patient associated with HIV-positive TB was likely to be two-fold greater than the costs incurred by HIV-negative patients ($946 versus $411 in Table 2-3 and Table 2-6).This is because HIV/AIDS and TB patients incurred a higher economic burden through out-of-pocket payments, and productivity loss.

The direct medical costs attributable to HIV/TB remained a sizeable burden for health care systems. These costs were estimated at an average of $298 per patient per year (including partial costs of ARV and TB drugs) (Table 2-6). The exemptions for TB-HIV fees only applied to drugs and not to the cost of associated hospitalization or other HIV-related drugs. Policy makers wishing to ensure that services are truly free should also consider reducing the price of these associated events.

The differences in average total healthcare costs across countries found in this systematic review were due to many factors such as differences in local settings, in the types of costs, and in treatment periods. The highest costs were found in Vietnam and the Dominican Republic. In the Dominican Republic, this is because health care facilities are further from patients' homes, resulting in higher transport costs. In Vietnam, this is because the length of TB treatment was longer than the other studies (8 month versus 6 months). Some studies included or excluded either TB or HIV related drugs or diagnosis. Three studies in this review focused on costs during the treatment period and two studies considered both periods: pre-treatment (pre-diagnostic) and during treatment (post-diagnostic). The costs of HIV-TB care in the pre-diagnostic period accounted for half of the total costs among patients in

either African or Vietnam implying that social support should be in place for those just started treatment particularly for those with low incomes where they easily incurred catastrophic health expenditures.

Given the estimated average costs, in Vietnam in 2014 the total treatment cost to cover 3,875 HIV and TB co-infected patients was likely to be $4 million. At the moment, the Vietnamese government only provides just over half of resources needed for current TB control (58% or $29 million, excluding OOP spending). The Global Fund (GF) and other private donors provided the remaining monies [94]. When the GF is cut in the future, the social health insurance is expected to cover a large part of this cost. Although political commitment to sustain free TB treatment is strong, whether the current approach will achieve this target in the future remains unclear.

The HIV-associated TB patients in Vietnam might incur potentially higher treatment costs than the estimated figure provided here due to two factors. The collaboration between the programmes for HIV and TB treatment in Vietnam have been known to be weak. While TB treatment sites are available in all districts, treatment sites for HIV are limited. Cross-referral between TB service and HIV service is currently the national strategy. However referral remains weak in practice with a substantial number of patients lost between referral and linkage to care [81]. Vietnamese policy makers might consider promoting greater integration of HIV and TB services to facilitate access that can reduce costs and make the services affordable to affected persons in such resource-poor settings.

Quality assessment of costing methods:

Using the CHEERS costing guideline, my review found that although data was collected from a large number of patients, statistical analyses were insufficient in most studies. At the least, descriptive statistics, for example the mean and median

values, standard deviation (SD), minimum and maximum values should be presented. The majority of studies did not conduct sensitivity analyses when they collected data from survey or facility based interviews when estimating patient costs. These technical limitations reduce the credibility of the research. No studies focused on assessment of costs for different patient sub-groups. Methodological variation across costing studies was significant in almost every costing category. Significantly, no studies focused on estimating the costs of treating extra-pulmonary TB patients; a group that is particularly likely to have serious sequelae as a result of their diseases, which likely incur greater costs. More research is urgently needed in this area to better understand how these treatment costs are affected by different degrees of TB severity and hospitalization.

Using the CHEERS guideline, I identified several key costing methodological issues (for example the bias of different data collection methods) in Vietnam in specific and in LMICs in general that suggest further standardisation to develop a set of costs that can be used globally:

First, different approaches to costing and data collection methods hindered our ability to observe cost drivers and analyse trends such as drug costs over time. For HIV-TB costing studies, costs were collected from patient interviews in 3 of the 5 studies that included a patient perspective [77,88,90] Data sources from patient interviews were subject to many forms of bias and measurement error. In the other two studies, cost data were retrieved from patient hospital registration.

For the meningitis and HIV costing studies, the sparse availability of primary data limits the statistical analysis. Data were collected mainly from 2 methods: review of patients medical records and personal interviews with patients and their caregivers following a structure questionnaire[111]. Cost analyses of inpatient care for HIV-associated disease, based on empirical data, in Vietnam seemed to be rare.

Three HIV costing studies in Vietnam [80,82,83] were unable to evaluate cost per bed-day specific to the hospitals due to lack of access to the hospital accounting system .

Second, the lack of reporting of disaggregated costs and resource quantity was an issue for HIV and HIV-TB treatment costs. Only 1 HIV costing study [109] and 1study on HIV-TB costing [90] in this review conformed to the ingredient approach to costing but techniques were not clearly described, and resource quantities and unit costs were not separately presented. In some studies, costs were determined by making assumptions about resources needed to treat HIV or TB according to national guidelines [80,109].

Third, methods for calculating productivity losses were not clearly explained in more than one-third of the studies that included these costs. The inclusion of productivity costs related to paid work in economic evaluations taking a societal perspective is generally acknowledged. However it is not clear whether productivity changes in paid work due to absence from work (absenteeism) or because of reduced productivity while at work (presenteeism). Additionally, most of the studies reported productivity losses limited to paid work only [77,112] and did not consider unpaid work although unpaid work was clearly an important source of economic value [113]. Three types of unpaid activities were distinguished from Bill and Melinda Gates reporting guidelines [114]: household work (e.g., cooking and cleaning), care work (e.g., taking care of children, helping friends or family with cleaning and personal care), and volunteer work (e.g., helping out in a commodity center or a sports club) [115]. Despite unpaid work's recognized importance, it was omitted from the vast majority of economic evaluations, even in studies that claimed to take a societal perspective. There is the need for complete

and validated measurement instruments for unpaid work to ensure that all productivity losses are measured.

Fourth, some other cost issues still remain. The year of cost data in 8 out 9 papers and the main cost categories were inadequately reported in 80 % of papers. Only about 60 % of studies presented descriptive statistics showing the spread around the mean cost values.

2.5.2 **Cost –effectiveness studies on timing of ART in HIV patients with other opportunistic infections**

2.5.2.1 Introduction

The timing of ART when patients present with opportunistic infections such as TB has been a medical conundrum for some time, which has recently been addressed by large randomised controlled trials. However, the question of timing goes beyond the medical into the economic - national and international policy-makers need to know the costs and the cost-effectiveness of starting HIV treatment during TB treatment in order to inform health policy decision making.

Starting early ART during TB treatment could increase cost, because more people receive ART with its material and monitoring costs, and its potential adverse events (side effects). Economic evaluation can help inform decision making regarding the scale-up of early ART in resource-limited settings and determine the most efficient allocation of resources. This review aims to assess the cost-effectiveness of different timing of ART initiation for patients co-infected with TB or other opportunistic infections.

2.5.2.2 Methods

Search strategy and inclusion criteria: : The investigators conducted the systematic review in accordance with the search strategies that were used for the CHEERS database developed by the International Society for Pharmacoeconomics and outcomes research (ISPOR) for costing and QALY. I searched for published articles addressing the cost effectiveness of initiating ART at different time points during treatment for HIV-TB co-infected patients or patients co-infected HIV with other opportunistic infections in developing countries between 2000 and 2014. I searched journal text using the following terms: 'tuberculosis' OR 'tuberculosis/HIV' OR 'meningitis/HIV AND 'cost-effectiveness' AND 'developing countries' AND 'ART" using the electronic online databases PubMed, Social Science research network (SSRN) and SOLO (Oxford University). Full details of the search strategy and terms are given in Appendix 2. The search was limited to review studies, peer-review papers, and international reports. Specifically, studies were eligible for inclusion in the current study if they met the following criteria: (1) study design: RCT; (2) population: HIV-positive adults (>13y) who have a co-infection with probable or confirmed TB; (3) intervention: patients were assigned to either an early ART initiation group or a delayed ART initiation group, regardless of any combinations of ART and anti-TB drugs used.

Cost-effectiveness studies were judged using the CHEERs [53]methodological quality criteria. Studies included in this review measured both cost and effectiveness using primary or secondary data. Studies used standard methods for estimating costs and outcomes and reported the incremental cost-effectiveness ratios against endpoints relevant to health-related outcomes - for example, costs per DALY averted, or deaths averted or cases averted.

Data extraction and analysis: The following information was extracted from each of the identified studies cover three broad areas: 1) background information, descriptive data on the intervention or alternatives to it and the context, 2) methods

of evaluation used, 3) results and generalizability. Costs in the original studies were adjusted to the year 2013.

2.5.2.3 Results

Few cost-effectiveness studies have been reported for the timing of ART in HIV-infected patients with OIs. Two studies were found in this literature search, which investigated the cost-effectiveness of early ART in patients with acute OIs, excluding TB[116] and in HIV co-infected TB patients [93].

Sax and colleagues [116] used data from the AIDS Clinical Trials Group (ACTG 5164) study to demonstrate that early ART was cost-effective in patients with acute OIs, excluding TB in the United States. An HIV simulation model was developed to compare the strategies of early ART versus delayed ART. Patients had a mean CD4 count was 47cells/μL. The majority of patients (63%) presented to care with *Pneumocystis jirovecii*pneumonia (PCP) and non-PCP fungal infections (16%) and bacterial infections (12%). None of the simulated patients had active tuberculosis. The study found that in the early ART arm QALYs increased from 10.07 to 10.39. Lifetime costs increased from $385,220 with deferred ART to $397,500 with early ART, primarily because life expectancy increased, producing an ICER of $38,600/QALY. This positive ICER indicates that early ART in patients with acute OIs, excluding TB was cost-effective because this intervention improved survival, with no increase in treatment failure, complications of therapy and met US cost-effectiveness thresholds. Nevertheless, the findings of this trial were not relevant to HIV and TB co-infected patients, for whom the risk of IRIS may be higher than in patients with other OIs.

Naidoo and colleagues [93] used data from the SAPIT study. This study evaluated the costs and cost-effectiveness of three strategies which were the initiation of the ART within 4 weeks after the initiation of TB treatment (early treatment-

arm1),initiation of the ART within 4 weeks of the continuation phase of TB treatment (late treatment-arm2), or on completion of TB treatment (sequential treatment-arm3) for patients co-infected with TB and HIV. The SAPIT trial included mainly pulmonary TB and 4.4% of the TB patients were extra-pulmonary TB. This trial did not specify the number of TBM patients. The SAPIT trial found a 56% reduction in mortality in patients starting ART during TB treatment (arm 1 and 2) compared to patients completing TB treatment (arm 3). On the other hand, no differences in mortality was found between the initiation of the ART within 4 weeks after the initiation of TB treatment (early treatment-arm1) and the initiation of the ART within 4 weeks of the continuation phase of TB treatment (late treatment-arm2), except in patients with CD4 counts ≤50 cells/mm3.

As a result, the cost-effectiveness analysis was applied in the sub-group with CD4 counts ≥50 cells/mm3 to determine the optimal strategy. The similar costs and similar mortality were found between the arm 1 and arm 2 for patients with CD4 counts ≥ 50 cells/mm3.The median direct medical costs (excluding TB treatment) for patients with CD4 counts ≥50 cells/mm3 were $2,401 for arm 1 and$2,348 for arm 2 (2013 USD), p=0.05Wilcoxon 2 sample-test). The similar costs between arm 1 and arm 2 were because the higher costs of the ART in arm 1 were partly offset by the higher costs of laboratory tests in arm 2. The higher laboratory tests in arm 2 versus arm 1 were due to abnormalities found in safety laboratory results but this study did not explain what these abnormalities were. In contrast, this study indicated that patients in the late treatment arm (arm 2) had the lowest number of hospitalizations, serious adverse events, and IRIS, which were deemed as cost drivers in the treatment cost of HIV and TB co-infection. When undertaking the cost-effectiveness analysis, arm 1 was dominated by arm 2 because patients in arm 1 had slightly higher mortality and incurred slightly higher cost than arm 2.

While patients in arm 3 experienced the cheapest costs because of shorter ART duration, they had the highest mortality. Incremental cost per death averted in moving from the sequential (arm3) to the late treatment (arm2) was $5,358. Arm 2 was considered to be a cost-effective strategy as this ratio was below the annual GDP per capita in South Africa in 2009 ($5,758). The conclusion is that delaying ART until the end of intensive phase of TB treatment (arm 2) for HIV co-infected TB patients with CD4counts ≥50 cells/mm3 was the most cost-effective strategy.

2.5.2.4 Discussion of cost-effectiveness studies:

Only one study was found to evaluate the cost-effectiveness of different timing of ART initiation in TB therapy for co-infected HIV-pulmonary TB patients with CD4 counts ≤200 cell/μL, but not for HIV-TBM patients[93]. This study suggested that late initiation of ART after the intensive phase of TB treatment (Arm-2) was the optimal strategy for patients with CD4 counts ≥50 cells/μL especially in resource-constrained settings.

This study [93] contained some limitations that require future research. The costs included mainly hospitalization costs and did not consider non-medical costs such as transport, guardian costs, or the income lost (the time costs incurred by patients were travelling to receive treatment in a primary hospital).No adjustments were made for censored cases. This study used unsophisticated methodology to compare differences in costs – namely the -Wilcoxon 2 sample-test to deal with skewed cost data[117]. The health outcomes of this study were measured in life years gained not the QALYs gained. Therefore this study did not capture the patient's quality of life, such as changes in morbidity caused by the adverse events arising from implementing early ART. The uncertainty of the cost-effectiveness was not assessed by more advanced methods such as acceptability curves [118].The fact that these studies used suboptimal methodologies may have led to inaccurate

estimates of both treatment costs and the health effectiveness of initiating ART during TB treatment.

2.5.3 **Quality of life studies on ART in HIV-infected patients in general and in HIV patients with TB**

2.5.3.1 Introduction

Since the advent of antiretroviral therapy, HIV-infected patients' quality of life has been greatly improved. As a result, health-related quality of life (HRQL) has become an important measurable outcome of HIV treatment, in addition to the incidence of opportunistic infections and time to progression to AIDS or death [119]. The quality of life is often interchangeably known as health-related quality of life (HRQL). HRQL is a broad term, which commonly reflects health dimensions ranging from physical health, mental health and function, to social and role function and general well-being. To better understand the disease burden, the objective of this section is to systematically review studies that evaluated HRQL of advanced- HIV patients and patients who are co-infected with HIV and TB using the EQ5D measurement tool from 2005 to 2013. TheEQ-5D questionnaire was selected because this is the instrument used in the trial that I analyze in the next chapter. In this review all references will be dedicated to the three level version of EQ5D-3L.

2.5.3.2 Methods of review

Literature search and study selection

The investigators conducted the systematic review in accordance with the search strategies that were used for the CHEERS [75].I systematically searched the peer-reviewed literature in two electronic databases: PUBMED and SOLO Oxford University from 2000 to 2014. Studies were included if 1) they used the EQ5D preference-based instrument to evaluate the quality of life of HIV-co-infected with TB diseases or TBM or advanced HIV or meningitis and 2) studies were conducted

in developing countries (where relevant). The search strategy included a combination of Medical Subject Headings (MeSH) terms for diseases “HIV-TB” or “meningitis”, “HIV/tuberculosis” or “tuberculous meningitis” or “HIV meningitis” and instrument names “Euroqol, EQ5D”. However, this preliminary search resulted in only 4 studies. I therefore expanded the search to include studies that had evaluated the HRQL of advanced HIV-infected adults (AIDS) taking ART in developing countries from 2005 to 2014.The search terms are presented in Appendix 3.

Instrument description

The standardized multidimensional self-completed questionnaire (EQ5D) was developed by the EuroQol Group that assessed five health dimensions: Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression [120]. The EuroQol Group has developed first the EQ5D 3-levels in which each of health dimension contained three levels, ranging from ‘no problems’ to “some problems” and to ‘extreme problems’. There were 243 health states for all possible combinations. EQ5D health states were then transformed into a single index score by applying general population preference weights that were derived from US [121], UK [122] and other European countries using a choice-based method (Time trade off, TTO) (http://www.euroqol.org/about-EQ5D/valuation-of-EQ5D/EQ5D-3l-value-sets.html, accessed18th August 2016). The most widely used weights are the UK tariffs generated from a survey of 3395 adults in the United Kingdom [123]. This instrument is currently lacking the value set of preference weights for South African population and it is relevant because I reported the South African studies. The preference weights have been derived for Thailand population [36]but not for Vietnamese. An EQ5D utility score is anchored at 0 for dead and 1 for perfect health, with some sets of utility values also permitting scores below zero for health states considered to be worse than death. The EQ5D is accompanied by a

visual analog scale (VAS) that assesses overall health. VAS scores range from 0 (dead) to 100 (perfect health).A higher score of the EQ-5D reflects better quality of life.

Data extraction and analysis

Data collection from each study included information about the study setting, study design, sample size, clinical and demographic characteristics of respondents, mean or median EQ5D index scores and the VAS scores, methods of assessment, and the study limitations. Meta-analysis was not possible here as these studies examined the quality of life from different patients populations and as CRD's guidance on undertaking systematic review in health care [75] indicated that pooling results obtained from diverse non-randomised study types was not recommended. The meta- analyses are appropriate for those studies that evaluate similar interventions in near identical participant populations. Hence, tables and narrative synopses were illustrated to synthesize findings. Quality of life studies were judged using the CHEERS [53].

2.5.3.3 Results

I screened titles and abstracts of 300 non-duplicate citations of which 6 studies were assessed in full text (Appendix 4 for flow chart of the search). I found no studies evaluating the quality of life of patients who were co-infected with HIV-TB or with HIV-TBM using the EQ5D measurement. Therefore, this review presents six studies that assessed the quality of life of advanced HIV/AIDS or meningitis patients using the EQ5D measurement (Figure 2-5, Figure 2-6 and Table 2-9).

Table 2-9: Summary of quality adjusted life year studies on HIV/TB patients in developing countries

First author, year, references	Country of origin	Study duration	Population	Sample size	Study type	EQ5D index scores	VAS scores
Tran (2013) [124]	Vietnam	1 year	HIV individuals taking ART	225	Observational	0.88	65.2
Tran (2013) [124]	Vietnam	1 year	HIV patient not yet required ART	175	Observational	0.9	69.3
Kittikraisak (2012) [125]	Thailand	2- 3 months	TB on treatment	32	Observational	0.69	80
Kittikraisak (2012) [125]	Thailand	2- 3 months	MDR-TB on treatment	11	Observational	0.51	60
Kittikraisak (2012) [125]	Thailand	2- 3 months	TB cured	32	Observational	0.88	85
Kittikraisak (2012) [125]	Thailand	2- 3 months	Any HIV	49	Observational	0.73	80
Kittikraisak (2012) [125]	Thailand	2- 3 months	TB with HIV on treatment	49	Observational	0.67	70
Kittikraisak (2012) [125]	Thailand	2- 3 months	Any TBC/HIV cured	49	Observational	1	80
Louwagie (2007) [126]	South Africa	70 (IQR 38.5–90) days.	HIV WHO stage 4 awaiting ART	268	Observational	0.69	62
Louwagie (2007) [126]	South Africa	71 (IQR 38.5–90) days.	HIV WHO stage 4 receiving ART	103	Observational	0.8	66
Sakthong (2014) [32]	Thailand	2 months ART	Asymptomatic HIV (17) Symptomatic HIV (72) AIDS (121)	210	Observational	0.56	
Solomos et al (2013) GBD [25]	4 countries		HIV-TB		A mix of observational, clinical trials	0.409	NA
Kulpeng et al (2013) [127]	Thailand	2010 to 2011	Meningitis children aged from 4 years to 10 years old		A hospital-based cross-sectional survey	0.1	35

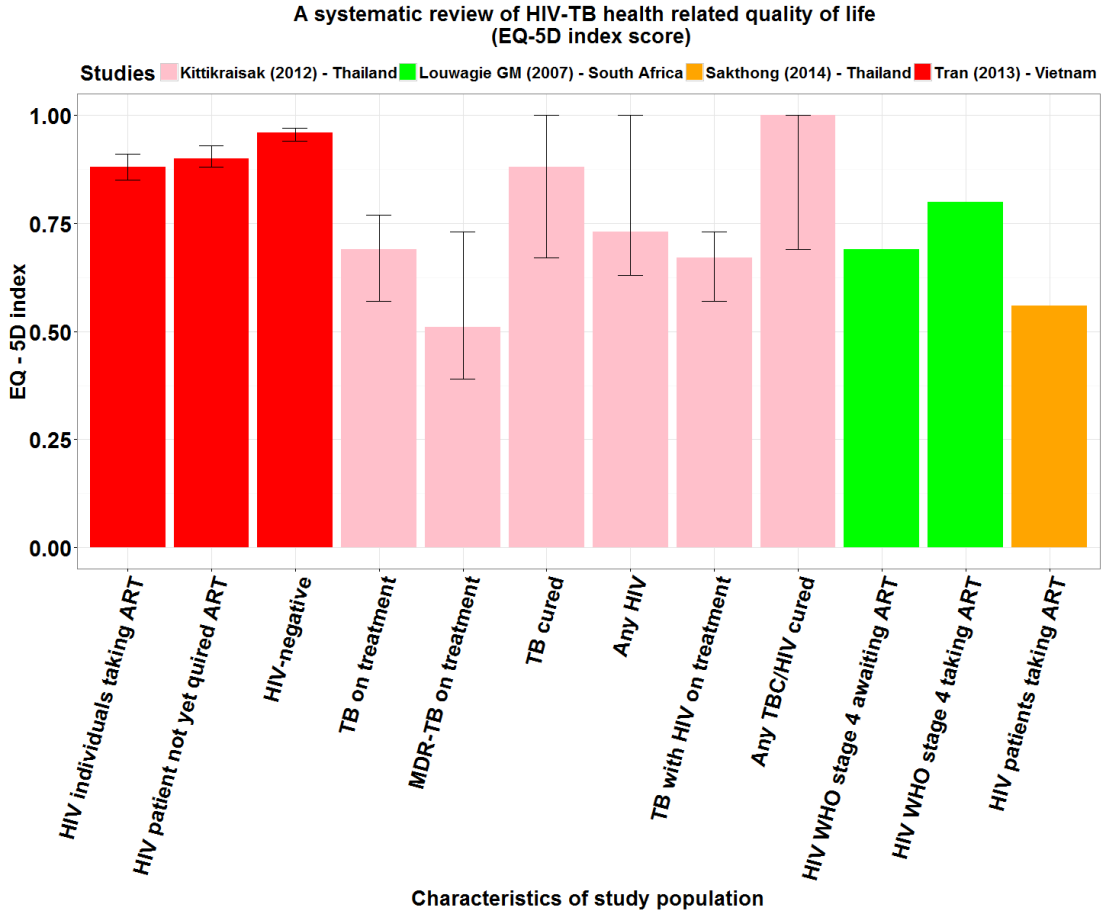


Figure 2-5: Systematic review of HIV/TB health-related quality of life studies (EQ5D index scores. The colours of the bar correspond to different studies in the systematic review including Louwagie (2007) [126] South Africa (green), Sakthong (2014) [32] Thailand (orange), Tran (2013) [124] Vietnam (red), Kittikraisak (2012) [125] Thailand (pink). The y-axis indicates the mean EQ5D index scores across studies ranging from -0.59 to 1. The x-axis presents the characteristics of study population. The min and max of the EQ5D index scores were presented as the error bar around means. Two studies Louwagie (2007) [126] and Sakthong (2014) [32] did not report the uncertainty around the EQ5D scores.

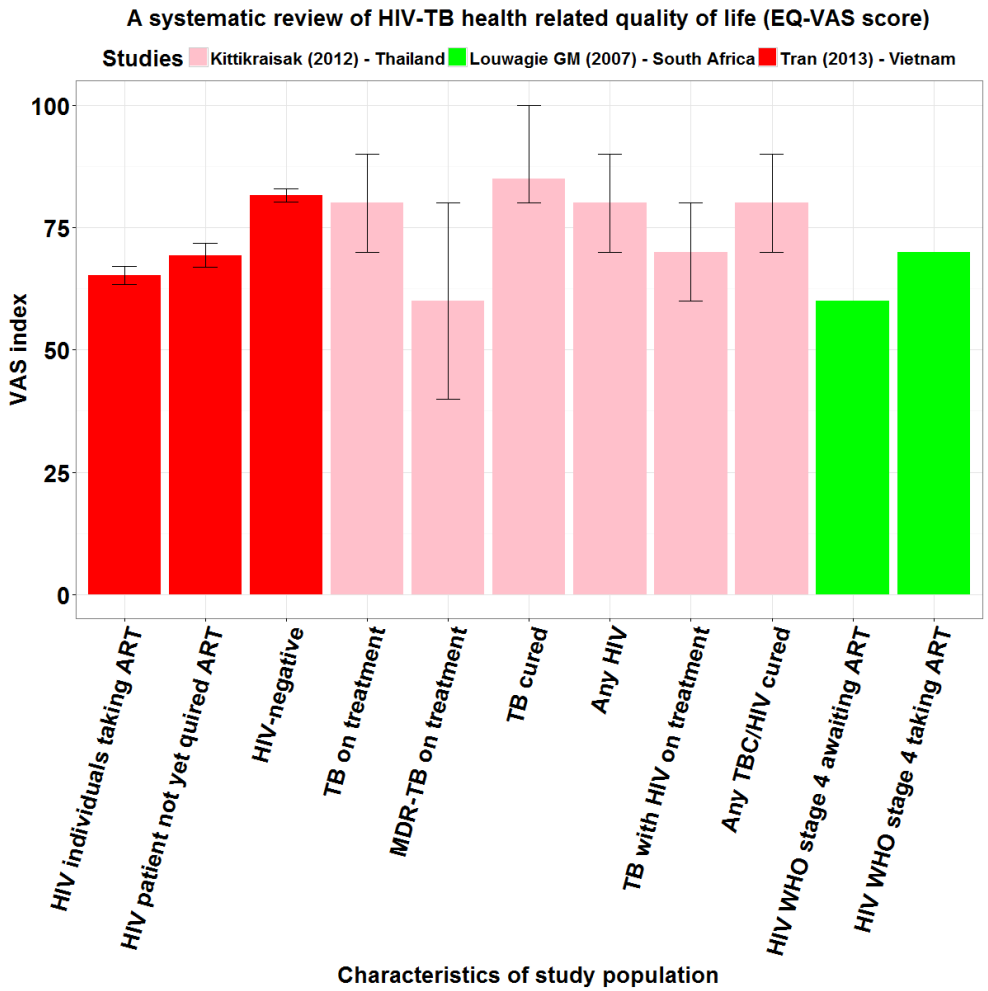


Figure 2-6: Systematic review of HIV/TB health-related quality of life studies (EQ-VAS index scores. The colours of the bar correspond to different studies in the systematic review including Louwagie (2007) [126] South Africa (green), Tran (2013) [124] Vietnam (red), Kittikraisak (2012) [125] Thailand (pink). The y-axis indicates the mean EQ-VAS index score across studies ranging from 0 to 100. The x-axis presents the characteristics of study population. The min and max of the EQ-VAS index scores are presented as the error bar around means. Louwagie (2007) [126] did not report the uncertainty around the EQ-VAS scores

Studies with utility estimates

A prospective observational study from Thailand demonstrated significantly lower HRQL in HIV infected pulmonary-TB patients compared to either pulmonary TB patients or HIV-infected patients using the EQ5D and VAS instruments [125]. The EQ5D utility index scores were derived from the Thai population in which these scores normally ranged from -0.45 (worse than death) to 1 (perfect health). The Thailand study found that the median EQ5D score and VAS score were 0.69 (80) for 32TB patients receiving TB treatment; 0.88 (85) for 32 cured TB or multiple drug resistance (MDR–TB); 1 (80) for TB/MDR-TB with HIV cured. The median EQ5D and VAS scores were lower for MDR-TB on treatment (0.51 and 60) and for HIV-infected patients at any stage who had not been diagnosed with TB (0.73 and 80) and for TB with HIV patients on TB treatment (0.67 and 70). The differences in health utility across medical states were warranted ($p<0.01$) after adjusting age and household monthly income using the multivariate Tobit regression analysis. More severe health utilities occurred during TB and HIV treatment than the other groups due to some TB symptoms and adverse events from HIV and TB drug interactions.

In contrast to the previous study, a further study from Thailand [32] found a lower EQ5D index score for HIV outpatients who had been taking the ART for an average of 4.3 months. The Thailand tariff was used. The mean EQ5D scores were associated with 0.56 (+/-0.26), meaning that HIV/AIDS and ART decreased the patient's quality of life by 54% from their healthy life. The study population included 17 asymptomatic HIV, and 72 symptomatic HIV, and 121 AIDS patients.

Initiating antiretroviral drugs during the first 3 months was likely to cause anemia, hyperlipidemia, lipodystrophy, and hepatitis in a quarter of the patients. This study did not report the VAS scores and did not specify whether the AIDS patients had any opportunistic infections. Regarding reliability, the EQ5D was considered highly reliable (Cronbach alpha =0.70-0.85).

A cross-sectional study from Vietnam [124] demonstrated that AIDS patients in Vietnam were associated with poorer HRQL than patients with early stage HIV. Among 400 HIV-positive patients, 56.3% were at AIDS stage and receiving ART, and 43.8% were asymptomatic or at earlier stages of HIV and therefore they had not yet met the criteria for treatment. The study found that adjusting for age and gender using multivariate linear regression, the average (mean) EQ5D and VAS scores in those with early HIV infection or asymptomatic were higher than AIDS patients taking ART (0.90; 69.3) versus 0.88 (65.2) (p=0.027) respectively. People with AIDS taking ART experienced significantly more pain/discomfort than earlier HIV stages.

Louwagie and colleagues [126] demonstrated that patients with AIDS receiving ART for a period of 2 months had significantly higher EQ5D index scores than a matched cohort of patients who awaiting ART(Louwagie et al. 2007). A total of 371 patients were interviewed (268 on treatment and 103 awaiting treatment) in public sector facilities in South Africa. Patients included in this study had a CD4 count below 200 cells/μL or were WHO stage 4 were eligible for initiating ART. The UK tariff was used in this study. Patients awaiting ART reported more problems such as pain/discomfort, depression/anxiety, mobility, with a mean

EQ5D (VAS) score of 0.69 (62) than patients receiving ART [mean EQ5D (VAS) score was 0.80 (66)]. The differences were significant (p=0.01) after adjusting for job and assistance from others using the multiple test regression.

The results of the review confirmed that EQ-5D data were currently available for HIV-TB as well as for advanced HIV/AIDs [125]. (GBD 2013) [128] [25] reported that HIV co-infected TB patients have an average disability weight of 0.408 (95% UI 0.224 to 0.454). The GBD 2013 did not provide any disability weights for meningitis. Nord et al (2015) [30] published comments in the Lancet 2013 arguing that the GBD lacked good data for severity distributions, and this could substantially reduce reliability of population disease burden estimates.

A hospital-based cross-sectional survey was conducted in 2010 [127] to evaluate the health outcomes of children with meningitis-related diseases aged between five to 14 years in seven tertiary hospitals in Thailand. The EQ5D and EQ-VAS and the Health Utilities Index Mark 2 (HUI 2) were applied to both paediatric patients (self-assessment) and caregivers (proxy-assessment) using the Thai tariffs. The EQ-5D scores for meningitis paediatric patients was 0.1 (0.05 to 0.22) and EQ-VAS scores was 35 (20 to 50). The EQ-5D yielded the lowest HRQL scores compared to other instruments in acute diseases. This study concluded that the EQ-5D in particular may not be sufficiently sensitive for measuring HRQL in patients with sensory impairment as it did not include a sensory dimension in the questionnaire.

2.5.3.4 Discussion of quality of life studies

The generic EQ5D questionnaire has a shorter interviewing time compared to HIV-specific measurements [35] and has been widely used in clinical trials to facilitate comparisons between diseases. Some important methodological issues of the EQ5D instrument have been subjected to areas of controversy, such as their sensitivity to the disease or the treatment, and the appropriateness of this tool in different HIV populations[129].

Four studies in this review indicated that the EQ5D was responsive to changes in clinical condition in the intended patient population and gave some implications about the feasibility and reliability of the instrument for both HRQL assessments and ART services. HIV infected TB patients had significantly lower HRQL than either TB patients or HIV-infected patients, indicating that impaired health utility occurred during TB and HIV treatment[125]. This highlights the fact that the EQ5D and EQ-VAS instruments can differentiate health utilities among TB patients regardless of HIV infection. In addition, this review suggests that the EQ5Dscores were not significantly related to both CD4 levels and viral loads [32]implying that these values did not reflect patient's concerns over their adverse drug effects of ARV drugs and HIV symptoms.

Furthermore, the EQ5D also showed itself may not be responsive to the small to medium changes in health status between consecutive follow-up visits a month apart. The possible explanation is that only the mental health recovered much within a month, but not the physical health, meanwhile the EQ5D questionnaire contributed mainly to physical health (mobility, self-care usual activity and pain/discomfort. Consequently, the EQ5D tool might not be sensitive enough to

capture the improvement in health in terms of mental health, resulting in possible overestimation of patient's HRQL.

The EQ5D and EQ-VAS instrument are both responsive to HIV/AIDS progression. AIDS patients in Vietnam had poorer HRQL scores than those in the early stages of HIV infection as these patients experienced more problems in anxiety/depression and pain/discomfort[130]. However, the stratification of HIV stages in the Vietnamese study was distinguished based on those who were qualified to receive ART or not. This indicator did not sufficiently reflect the disease progression of participants. The EQ5D also showed that the ART improved the HRQL of patients with AIDS receiving ART for a period of 2 months compared with a matched cohort of patients who awaiting ART [126].

The studies in this review contained some limitations that must be acknowledged. One study only reported median values, which were useful in assessing the distribution of the data but did not permit the total quantum of health gain to be computed. The valuations for the EQ5D scores were mainly derived from the UK population. Valuations in a South African population have not yet been made available and may differ because of socio-demographic characteristics and cultural attitudes towards health and disease. The assessment of EQ5D was based on outpatients and did not capture all relevant dimensions of HRQL related to opportunistic infections such as HIV-meningitis. Most importantly, this review lacked studies that evaluated the responsiveness of the EQ5D to changes in therapy, occurrences of adverse event, AIDS-defining events, disease severity (CD4 levels, viral load) or different duration of ART. Based on these findings, the

recommendation of this review is that the EQ5D should be used in a trial in conjunction with a HIV-disease specific measure to get a more detailed picture of factors affecting the patient's HRQL.

2.6 **Conclusion of chapter 2:**

To date, evidence about the costs and the cost-effectiveness of initiating ART during TB treatment is scare. The evidence suggests conflicting results regarding the cost-effectiveness of starting ART early. The next chapter is going to conduct the economic evaluation of our trial that compared the different timing of ART during TB treatment in HIV and TBM co-infected patients. The findings of this health economic analysis will contribute to the currently lacking evidence base about the costs and the QALYs of HIV-TBM patients undertaking ART during TB treatment.

Chapter 3**: Health economic assessment of the timing of antiretroviral therapy in human immunodeficiency virus (HIV) associated tuberculous meningitis in Vietnam**

3.1 **Introduction to the study**

WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommend initiating ART immediately after the start of TBM treatment regardless of WHO clinical stage or CD4 cell count for people with active TB disease who are living with HIV [131]. These guidelines are based on the evidence from three randomized clinical trials[60,61,71]. These three trials found that for people with TB and severe immunodeficiency (CD4 counts≤50 cells/mm3); starting ART early (4 weeks after TB treatment) has a clinical benefit compared with deferring ART treatment (8 weeks after TB treatment). However, as stated in the previous chapter few patients in these three studies had TBM – most had pulmonary TB or some other form of extra-pulmonary TB. The pathophysiology of TBM is somewhat different to these conditions since nervous tissue has extremely poor regenerative capacity and, being enclosed in non-expansile box (the skull) any inflammation with resultant brain swelling, that can occur due to inflammation as a consequence of immune reconstitution, could result in severe outcomes.

Our randomized controlled trial of early versus delayed ART in HIV infected patients with TBM was based in 2 hospitals in Ho Chi Minh City[57]. Our trial recruited 256 patients (127 in the immediate ART and 126 in the deferred ART)

between 2005 and 2007. The primary endpoint was survival until 9 months after randomisation; our trial found that there was no significant difference in survival between the patients receiving early ART treatment (1 week after instigation of TBM treatment) versus those receiving late ART treatment (8 weeks after instigation of TBM treatment) (HR, 1.12; 95% CI, .81 to -1.55; P = 0.5). Patients in the early ART arm suffered more grade 4 adverse events (102 vs 87; p=0.04). Immediate ART was also associated with a higher frequency of patients with 4 adverse events during the first 2 months (77 vs 59, p=0.03), indicating that early ART initiation may be detrimental in this group.

Our recommendation is that ART should be delayed until 8 weeks after beginning TBM treatment, unless there were compelling other reasons to start earlier. As a result, a cost-effectiveness analysis based on this clinical trial was conducted to help guide policy recommendations on choice of optimal strategy for patients co-infected with HIV and TBM, especially in resource-constrained settings. There have been no previous studies that assessed the costs and the cost–effectiveness of different timings of ART to treat HIV and TBM.

To provide this information, we examined the cost-effectiveness of immediate versus deferred antiretroviral therapy in HIV-associated TBM patients in a Vietnamese context. The costs and outcomes of these 2 health interventions were compared from two perspectives: a) the Vietnamese health system perspective (hospital and patients, and related care givers) and b) a societal perspective (including productivity losses). While the results of the trial might lead one to assume that immediate ART is unlikely to have any economic benefit because of the increased risk of adverse events in the early arm, it may be that there are hidden costs of deferring treatment. For example, deferring ART might cause patients and

their carers to incur greater income losses, as a result of a greater need for carer's assistance and time accompanying patients during hospital visits. Furthermore, there could be possible quality of life differences associated with adverse events. Therefore, I undertook this health economics analysis.

3.2 **Methods**

3.2.1 **Overview of economic evaluation of timing of ART to treat HIV-associated tuberculous meningitis patients (EC study)**

The EC study was performed alongside a randomized, double blind, placebo–controlled trial of immediate versus deferred antiretroviral therapy in patients with HIV-associated tuberculous meningitis (TBM). The paper of this trial is presented in the Appendix 19. The trial was conducted between 2005 and 2007 at 2 sites in the south of Vietnam: the Hospital for Tropical Diseases, and Pham Ngoc Thach Hospital in Ho Chi Minh City, the referral hospitals for HIV and TB respectively.

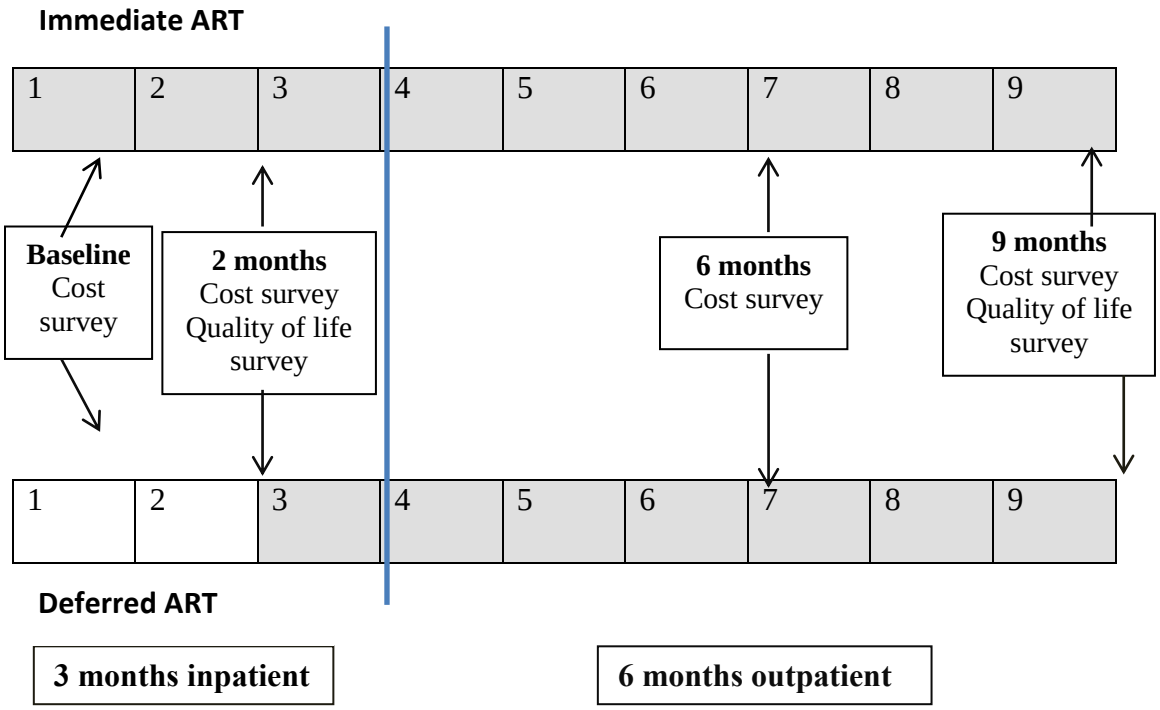
The study population consisted of adult HIV positive patients (aged≥15 years) with a clinical diagnosis of TBM, who consented to enter the study. The clinical trial enrolled 127 patients in the immediate ART group and 126 patients in the deferred ART group. Not all patients enrolled in the trial were available for analysis in the economic study; a total of 204 participants agreed to enroll in the health economic study (EC study): 101 participants in the immediate ART treatment group and 103 participants in the deferred treatment group. The main reasons for lower participation is that the health economics study started after the clinical trial and early mortality meant some patients died before recruitment to the EC study. All patients had a baseline CD4 cell count of ≤ 200 cells/μL and therefore were treated with ART according to the Vietnamese national guidelines (Vietnamese guidelines

for HIV/AIDS diagnosis and treatment 2005). These patients underwent stratified randomization to one of two interventions: immediate ART or deferred ART. Immediate ART received treatment within 1 week of randomization. Deferred ART received placebo for the first 2 months of treatment and then commenced ART.

The ART regime used in the trial was a combination of AZT (zidovudine) + 3TC (lamivudine) + EFV (efavirenz). All patients also received standard antituberculous chemotherapy and adjunctive dexamethasone, according to the local guidelines. The treatment dosage was stated in the paper [57]. All patients were monitored daily as inpatients for 3 months, then monthly as outpatients until 9 months. A final follow-up visit took place at 12 months. The primary endpoint for the clinical trial was mortality at 9 months.

The EC study included assessment of the costs incurred and health outcome for subjects in both arms of the trial. Costs were collected through questionnaires that were administered by Vietnamese nursing staff at defined time points during the clinical trial: baseline (within 1 week of study entry), 2 months, 6 months, and 9months. Health outcome assessment was made using the Euroqol EQ5D questionnaire administered at 2 and 9months[120]. The questionnaire is presented in the Appendix 6. The timeframe for comparison was the 9 months period from randomization and therefore no discounting was required [132]. The timeline of the study is presented in Figure 3-1.

Figure 3-1:Timeline of the study



3.2.2 **Data descriptions**

This section provides the definition of the data and the data sources, beginning with costs, and then health outcomes and clinical characteristics.

3.2.2.1 Costs

This study classified costs into four main costs: Hospital healthcare costs, patient healthcare costs, productivity losses, and societal costs

Hospital healthcare costs: This is defined as the costs arising from resources used within the hospital. These costs were collected from each patient's hospital bill. These healthcare costs were collected up until the end of each patient's treatment period. The 'treatment period' is the time from when the patients entered the trial until they completed the study at 9 months (which was also known as administrative censoring at 9 months), or until they exited from the trial due to death or loss to follow up. Healthcare costs reflected each patient's treatment

period, which was recorded in days. During inpatient stays, patients were reviewed at least two times every day by the doctors on the ward. During the outpatient phase, patients visited the hospital for follow-up on a monthly basis. The patients were seen by the study doctors once per month during the outpatient phase. Patients could also attend the hospital with the scheduled study visits according to clinical need. This could lead to hospital admission and therefore their unplanned outpatient visits could result in an inpatient stay. The treatment period took this into account and covers the patient's total inpatient days and total outpatient days.

Hospital healthcare costs were divided into 18 different categories (Table 3.1). The antiretroviral drug therapy (ART) and the anti-tuberculous drugs (TB) were financed by the Vietnamese national health programs for HIV/AIDS and TB care. The clinical trial sponsored the remaining hospital healthcare costs for patients which were antibiotics, other medicines, blood tests, microbiological diagnostic tests serological tests CD4 count test, radiography (x-rays, ultrasound, CT-Scan, MRI), administrative costs related to examining at hospitals, bed costs, procedure, blood transfusions , devices, oxygen, food expenses , and care fee when patients were hospitalized. The patients did not pay any hospital healthcare costs while they participated in this trial.

Table 3-1: Hospital healthcare costs:

The items of main cost	**Cost explanation**
1.Antiretroviral drugs (ARV)	ARVs were either purchased from the drug company (efavirenz, Merck) or donated by GSK (Combivir). These costs reflected the market costs at the time of the study. The antiretroviral regimen was oral zidovudine (GlaxoSmithKline) at a dose of 300 mg twice daily, lamivudine (GlaxoSmithKline) at a dose of 150 mg twice

The items of main cost	Cost explanation
	daily (as a fixed-dose combination tablet), and efavirenz (Merck) at a dose of 800 mg once daily (if taken with rifampicin) or efavirenzat a dose of 600 mg once daily (if taken without rifampicin).
2. Anti-tuberculous drugs (TB)	Vietnamese National TB Programme guidelines in 2005 [133] recommended that antituberculous treatment for tuberculous meningitis to be 9 months. The intensive phase employed isonazid, rifampicin, pyrazinamide and ethambutol for 3 months. After 3 months, pyrazinamide and ethambutol were stopped and the patient continued on rifampicin and isoniazid at the same doses for a further 6 months
3. Antibiotic	Any antibiotic were used in the treatment
4. Other medicines	Any other medication used in the treatment
5.Blood tests	Routine laboratory tests were monitored weekly as an inpatient and monthly as an outpatient. Blood samples for CD4 T-lymphocyte count and plasma HIV-1 RNA level were be monitored 3-monthly.Cerebrospinal fluid (CSF) samples were taken at 0, 1, 2, 3, 6 and 9 months.
6. Microbiological diagnostic tests including microscopy and culture, CSF test, blood culture, stool test, urine test…)	
7. Serological tests including HIV tests, anti HCV (hepatitis C), HIV-1RNA…)	
8.CD4 count test	
9.Radiography (x-rays, ultrasound, CT-Scan, MRI)	Patients had a chest radiograph performed on admission. A CT or MRI brain scan could also be performed if clinically indicated. Further imaging was performed in the event of a clinical deterioration
10.Administrative costs related to examining at hospitals	Consultation fees
11. Bed costs	Cost of occupying a bed in the hospital
12. Procedures,	Any procedures were involved in the treatment

The items of main cost	Cost explanation
13. Devices	Any medical devices were used in the treatment
14. Blood transfusions	Any blood transfusions were used in the treatment
15. Oxygen	Any oxygen therapies were used for hospitalized patients
16. Food expenses	The 'Food expenses' in this category were incurred for 111 hospitalised patients. These patients were fed by nasogastric tube as they were too ill to eat independently. Food expenses were not included in the calculations for the period after the patient was discharged from hospital.
17. Care-fee	The 'Care-fee' were the costs the patient's carers paid to stay at the carers' accommodation at the Hospital for Tropical Diseases while the patients were in the intensive care unit.
18. Other medical expenses	'Other medical expenses' were incurred as the hospital provided hospitalization certificates to patients at the time they were discharged from hospital and when they asked for consultations from different hospital departments.

Patient healthcare costs (including caregiver costs): These healthcare costs were paid by patients and caregivers on an out of pocket basis, and so these costs were not incurred by the hospitals. These health care costs were collected from questionnaires (Table 3.2). The questionnaire asked which costs were incurred during the week and the day of assessment prior to completion of the questionnaire. The questionnaire was administered at 4 time points: Baseline, 2 months, 6 months, and 9 months. At each of follow-up time points, patient healthcare costs were collected as weekly costs. These weekly costs were later adjusted to reflect the patient's treatment days. The cost adjustment method is presented later in this section. Patient healthcare costs were divided into seven categories.

Productivity losses: This cost information was recorded in the form of income lost. These costs were collected from questionnaires that asked about income lost that

the patient incurred when they came to today's assessment at the hospital at four different follow-up time points (Baseline, 2 months, 6 months, and 9 months. These daily costs were also adjusted to reflect the patient's treatment days. Productivity losses consisted of two categories. (Table 3.2)

Table 3-2: Patient healthcare costs and productivity losses (including caregiver costs)

The items of main cost	Cost explanation
Patient health care costs	
1. Medication costs	The 'Medication costs' refers to the costs that the patients paid for medications, fluids, and other health products that the patients incurred during the week prior to completion of the questionnaire.
2. Administrative costs related to examining at health clinics	The 'Examination costs' were the fees that the patients paid for consultations at the hospital or doctor's clinic during the week prior to completion of the questionnaire.
3. Other expenses	The 'Other expenses' included the costs of diagnostic tests during this illness prior to entry to the study and other costs (for examples: the costs of diapers) that the patients incurred during the week prior to completion of the questionnaire.
4. Patient's and care giver's food costs	Patient's and caregiver's food costs' refers to the average daily food costs that the patients and caregivers incurred during the week prior to completion of the questionnaire.
5. Patient's and care giver's transportation costs	The 'Patient's and care giver's transportation costs' were the costs that the patients paid for transportation to the hospitals and doctor's clinics and the caregivers paid for accompanying the patients to predefined follow-up visits during the week prior to

The items of main cost	Cost explanation
	completion of the questionnaire.
6. Assistance costs from family members, helper at home, nurse, friends, and others (other relatives, and hired helpers)	The 'Assistance costs' were the costs incurred by patient's caregivers who were family members, helper at home, nurse, friends, and others (other relatives, and hired helpers) in providing assistance to the patient during the week prior to completion of the questionnaire.
7. Accompany costs	The 'Accompany cost' consisted of the other costs that the caregiver's cost paid for accompanying the patients to predefined follow-up visits during the week prior to completion of the questionnaire.
Productivity losses	
1. Income lost for waiting and health exam for a today's visit	'Income lost for waiting and health examination for today's visit refers to the patient reported income lost as a result of time spent waiting and undergoing health examination for a hospital visit at each follow up time point
2. Income lost for accompanying to today's visit.	'Income lost for accompanying to today's visit refers to the caregiver reported income lost as a result of accompanying the patients to a hospital visit at each follow up time point.

Societal costs: This cost is defined as the sum of healthcare costs incurred by the hospitals, patients and caregivers, and productivity losses (Table 3.3). This cost was referred to as the unadjusted censored total cost. The societal costs were later adjusted for censored cases to obtain the adjusted censored total costs.

Table 3-3: Societal costs

The items of main cost	Cost explanation
1.Hospital healthcare	Costs were extracted from resources used within the

costs	hospital and included 18 different costs.
2. Patient healthcare costs	These healthcare costs were paid by the patients and their caregivers on an out of pocket basis and included 7 different costs.
3.Productivity losses	They were the income lost incurred by patients for waiting and getting health check-up from today's visit at the hospital and the income lost incurred by their care givers to accompany them to today's health assessment.

3.2.2.2 Health outcomes

Patient health outcomes in this study were measured in terms of quality-adjusted life years (QALYs). They are presented in Table 3-4 and are explained as follows:

Table 3-4: The health outcome data of this study

The items of health outcome (Quality adjusted life years)	**Health outcome explanation**	**Source**
1.Patient's health-related quality of life	'Patient's health related quality of life' included EQ5D utility scores and the Visual analog scales	EuroQOL EQ5D-3L questionnaire
2. Patient's survival times within the trial		Our clinical trial [57]

A patient's quantity of life is the patient's survival time within the trial and is collected from the clinical trial [74]

A patient's health-related quality of life comprises multiple health states (usually referred to as domains or dimensions) relating to both physical and mental capacity. These health states are evaluated by standardized questionnaires to which health utility scores are then attached. In this analysis, patients' health- related

quality of life was evaluated using the EuroQOL five-dimension questionnaire (EQ5D-3L), and a visual analog scale (VAS). In this study, these scores were derived from different tariffs obtained from population valuations from UK and Thailand samples that were on the scale of -0.594 to 1 and -0.454 to 1 respectively.

In addition to the 5 questions, respondents completing the EQ5D-3L reported their self-rated health on a vertical, 20-cm visual analogue scale (VAS) resembling a thermometer, where the endpoints (0, 100) were labelled ‘‘Best imaginable health state’’ and ‘‘Worst imaginable health state’’[120]. In this study, the EQ5D-3L questionnaire was distributed to patients in both groups at 2 months and at 9 months following their entry to the study.

3.2.2.3 Clinical characteristics

The data concerning the patient’s clinical characteristics were also used in this study (Table 3.5). These clinical data was collected from the clinical trial at baseline.

Table 3-5: Baseline clinical characteristics of study population

The items of data	The explanation of data
1. Participant’s characteristics	Gender(Male/Female), age, weight, temperature
2.Having previous TB	Whether participants had TB before (Yes/No)
3.TBM grade at baseline (I, II and III)	‘TBM Grade’ 1: GCS =15 with no focal neurology; Grade II = GCS 11-14 or GCS 15 with focal neurology or Grade III : GCS ≤10 . ‘TBM grade’ was assessed using the modified Medical Research Council TBM Grading. Glasgow coma scale (GCS) is a neurological scale which recorded the conscious state of a person [134].
4. TBM at diagnosis	TBM at diagnosis was classified as definite, probable, and possible according to the clinical trial.

5. Hospital sites	Pham Ngoc Thach hospital (PNT); Hospital of tropical disease (HTD)
6. Treatment types	Immediate ART; deferred ART
7. CD4 cell counts at baseline	A CD4 count ≤ 200 cells/μL is one of the qualifications for an AIDS diagnosis.

3.2.3 **Data adjustment**

Some adjustments were made to the costs and the quality adjusted life years before progressing to the analysis. The first step was the adjustments for missing data in both costs and quality of life data.

3.2.3.1 Adjustments for missing data

I used three steps to deal with missing data. Firstly, I determined the percentage of missing data in costs and EQ5D scores and VAS at any time points. Secondly the patterns of missing data were examined to determine whether data were) missing completely at random (MCAR), ii) missing at random (MAR), or iii) missing not at random (MNAR). MCAR is when the probability of missingness is independent of any characteristics of the subjects. MAR is when the probability a variable is missing depends only on observed variables. MNAR is when the probability an observation is missing depends upon information that is not observed, like the value of the observation itself [135,136]. The functions MICE packages in R were used to interpret the number of missing values and the pattern of these missing values .

Thirdly, after identifying the missing values in data, I used two methods to address missing values in costs, and EQ-VAS: complete-cases and multiple imputation. Complete cases analysis discards missing data at different follow-up time points. Specifically, subjects with one missing data at any time point were removed from

analysis at all-time points and the results calculated only for subjects with full information at all the time points. However, complete-cases analysis can lead to loss of information and deliver unreliable results. This approach should be limited to datasets with a small amount of missing data. If the missing costs are identified as MCAR, complete-case analysis will give unbiased results. However, when data are MAR, a complete-case analysis may lead to biased results because the analysis is not based on a random sample of the study population and therefore is not representative of the whole study group.

I applied a multiple imputation analysis (MI) to resolve these drawbacks. Multiple imputation followed the procedures set out by [137]. Chained Equations (MICE) were used to impute multivariate data based on joint modeling and conditional specifications. The selection of predictors was the baseline clinical data as presented in Table 3.5 and other patient healthcare costs and patient's time spent on transport and the care giver's time for accompanying the patients to health visits (Appendix 7). Next, based on Rubin's rule[136], the missing data was imputed *m* times and therefore *m (m=20)* complete data sets with the imputed values were generated. The m complete data sets were then combined together to produce the pooled data set. Each imputed value in the pooled data set was equal to the average of these imputed values in the m complete dataset. When reporting the results of the multiple imputation analysis, single pooled parameter estimates were calculated according to the steps guided by this paper [138]. First, a pooled estimate of *Q (the pooled statistics of interest for costs and effects)* based on the *M* imputed data sets was simply the mean of the *M* estimates. The pooled parameters of interest were a pooled (KMSA) mean of costs and QALYs for each treatment

arm and pooled (KMSA) mean differences in costs and QALYs between the two treatment arms.

$$\overline{Q}=\frac{1}{M}\sum_{m=1}^{M}\hat{Q}_m. \quad (1)$$

Secondly, the estimate of the overall variance (*T* of $\bar{Q}$) of the pooled parameters of interest consists of two parts, namely $\bar{U}$ the *within imputation variability* i.e. the mean of the squared standard errors within the imputed data sets:

$$\overline{U}=\frac{1}{M}\sum_{m=1}^{M}U_m, \quad (2)$$

and *B* the *between-imputation variability* caused by the differences in imputed values across the data sets

$$B=\frac{1}{M-1}\sum_{m=1}^{M}(\hat{Q}_m-\overline{Q})^2. \quad (3)$$

The overall variance *T* associated with $\bar{Q}$ then becomes:

$$T=\overline{U}+(1+M^{-1})B, \quad (4)$$

where the coefficient $(1 + M-1)B$ serves to correct for the extra variability due to the missing data.

The overall standard deviation was then computed by taking the square root of this overall variance. The overall standard errors can be computed by dividing the overall standard deviation by the square root of the number of imputed datasets. The overall standard deviation was presented in the trial-based economic

evaluation. The standard errors can be provided on request as there was not enough space for presenting these figures.

The pooled mean of the cost and QALYs for each treatment strategy then was used to estimate the ICERs using the standard approach [139]. To capture the uncertainty in the cost-effectiveness of each treatment, CEACs were presented to show the probability that immediate ART was more cost-effective than the deferred ART across the a range of WTPs for a QALY gained [140]. To my knowledge there have been no papers that explored the application of multiple imputation into a cost-effectiveness analysis involving two comparators, with the focus on the construction of CEACs [141–145]. Most health economic papers reported the use of multiple imputation but did not explicitly discuss whether the correct pooled statistics were employed, and whether the final results took account of this missing technique. A detailed discussion of this idea was presented in an unpublished paper [145]. In this paper, the pooling of mean costs and QALY into acceptability curve was described in detail [145]. This paper compared parametric and non-parametric methods for constructing CEACs.

In this paper [145], the first non-parametric method was proposed to combine *m* datasets resulting from the multiple imputation into one large dataset, and then 1000 bootstrapped samples of costs and effectives were generated from this pooled dataset to form CEACs. The second non-parametric method was executed by bootstrapping each dataset separately. These 1000 datasets were then combined for calculating pooled means in order to provide 1000 samples from which to construct the CEACs. However, these two non-parametric methods for constructing CEAC

were critiqued for not taking account of the between-imputation variance and therefore the uncertainty around treatment strategies may be underestimated because of this omission [145].

Therefore I decided to use the mixture of parametric and non-parametric method to construct CEACs from *m* multiply imputed datasets following multiple imputation, as presented in this paper [145]. This approach was considered to properly incorporate the between-imputation variance. Therefore, I implemented this approach based on the following steps. First, I explored the likely distribution for costs and health benefits in each of *m* imputed datasets. Second, a lognormal distribution was chosen to describe the cost and QALYs data in each treatment group. This distribution was informed by the pooled mean and a pooled standard deviation from the multiply imputed datasets, and therefore would include the between-imputation variance. By using these estimates to define a distribution for costs and health benefits, it was possible to repeatedly simulate the sample from the distribution 1000 times in order to obtain data equivalent to the bootstrapped information with which to construct the CEACs. Furthermore, I also explored the correlation between the costs and QALYs so that the subsequent samples randomly selected from each distribution reflected this correlation. By doing these steps, I aimed to demonstrate that once multiple imputation were employed to address the problem of missing data, the subsequent analysis such as CEAC properly reflected the multiple imputation procedure.

The economic data were only available for 204 patients and among these patients; there were three missing values in medication costs and eight missing values in EQ5D-VAS scores. Given a small amount of missing values, both complete cases

and multiple imputation were meant to provide similar results. The multiple imputation may not add much benefit for the cost-effectiveness analysis.

However, the multiple imputation were of a value in subsequent analysis of predicting missing values for 49 patients. The original randomized controlled trial had a sample size of n=253. The economic data were not available for 49 patients because out of them, 25 patients (n=11 patients in immediate ART versus n=14 patients in deferred ART) died before entering the economic project. The economic project was implemented a week after the onset of clinical trial. The other 24 patients refused to join the health economic project (n =14 patients for immediate ART and 10 patients for deferred ART). Therefore, 25 patients who died before entering the economic project were assumed to have zero costs and zero QALYs. The costs and QALYs of other 24 patients were treated as missing values and the multiple imputations were used to predict these missing data. Given greater amount of missing values, the multiple imputation approach was believed to give more accurate estimates in this analysis [136] because MI is considered as the best practice for dealing with missing data with a MAR pattern [135].

3.2.3.2 Adjustments for costs

This section presents two main adjustments that were made for costs.

Firstly, the ART drug costs in the hospital healthcare costs were adjusted. For patients whose treatment days were less than 2 months, the ART drug costs were set to zero. The reason for this is that, according to the protocol, in the first 2 months the patients in the deferred ART group received placebo, not the real ART drug. Therefore, these patients were supposed not to incur any ART drug costs s during the first 2 months. This issue arose from the fact that this was a blinded

randomized clinical trial. The hospital did not know the patients received the placebo drugs so they recorded ART drug costs for these patients in the first 2 months. For patients whose treatment days were greater than 2 months, the total ART drug costs were subtracted from the average 2-month ART drug costs in the deferred ART group. This approach was done because the study did not collect the ART drug costs daily for each patient. Therefore there was no information on ART drug costs at day 60 for each patient, but only the total ART expenses by the time the patients completed their treatment.

Average 2 month ART drug costs = each patient's ART drug costs in deferred ART / their treatment days to get each patient's daily ART drug costs. This was then multiplied by 60 days, and then was averaged out to get 2 month ART drug costs.

Secondly, weekly patient health care costs and daily productivity losses at 2 months, 6 months, and 9 months were adjusted to costs that covered each patient's treatment days:

The average weekly costs and daily costs were estimated conditional on the probability of positive costs:

The proportions of positive costs and the trend of weekly costs at baseline, 2 months, 6 months, and 9 months were identified. In this study, there were a substantial number of participants who reported not having incurred any healthcare costs by the patients and care givers or productivity losses. As a result, a small proportion of positive costs were obtained. This great amount of zero-cost observations might cause problems in regression analyses and result in unreliable

estimates of average costs. To solve this problem of multiple zeros, the analysis conducted a two-part model.

Two-part models were used to predict the average weekly patient healthcare costs and productivity losses, given that these cost categories exhibited a great number of zero-cost values. The first part of the model predicted the probability of having positive costs. For this part a logistic regression model, using a binary variable defined by whether the patient had positive costs, was employed. The second part was fitted by the use of a generalized linear model (GLM) to predict costs in the subset of patients whose costs is positive. The GLM model with log link and family "Gamma" was chosen. The log link function was chosen to model the log of arithmetic mean cost to deal with skewed cost distribution. The predicted positive costs were then obtained from the GLM model and were log transformed to represent the arithmetic mean of the weekly costs. Finally, the predicted weekly costs for all patients were derived by multiplying the predictions from the two parts of the model – the probability of incurring costs, and the level of costs if costs were incurred together. The predictors for patient healthcare costs and productivity losses at 2 months, 6 months, and 9 months were the same as those used for missing data (Appendix 8).

Next, each patient's predicted average weekly and daily costs were adjusted to costs that cover patient's treatment days.

Two groups of costs were used when making these modifications (Table 3-6). The first group of costs included 4 different cost categories: examination costs, accompany costs (caregivers), transport costs (patients &caregivers), and income lost for waiting &exam & accompanying (patients &caregivers). These costs were

adjusted based on the number of predefined study visits during each patient's treatment days. This is because these costs only emerged when the patients made these trips. According to the health economic protocol, all patients were monitored daily as inpatients for 3 months and then monthly as an outpatient until 9 months. Therefore, if a patient was alive until 9 months, the patients made 96 doctor visits in total. The assumption made was that the severity of patients' symptoms meant they were unlikely to be mobile and therefore would not be able to make any extra visits and therefore only incurred the number of visits specified in the protocol. Therefore, this study assumed that the patients could have 7 daily doctor visits per week during inpatient stay, and 1 doctor visit per month during outpatient stay.

The second group of costs encompassed four cost categories: assistance from carers, medications, food expenses (patients and caregivers) and any other expenses. These were adjusted based on the duration of the patient's treatment, irrespective of inpatient or outpatient stay. This adjustment was done because these were necessary services and patients needed them throughout the time they were in hospital. Food expenses were recorded on daily forms and were also adjusted. After adjustment, patient healthcare costs and productivity losses covering inpatient stay and outpatient visits were added together to cover each patient's total treatment days.

The limitation of this cost adjustment was that weekly costs collected from questionnaires were considered as the average weekly costs in each of three follow-up periods (from baseline to 3 months, 4 months to 6 months, and 7 months to 9 months). This might not be true in reality as the costs might behave differently every week.

Table 3-6: Adjustment for patient healthcare costs

Cost categories	Adjustment factor	Adjustment
1.Exam costs due to private doctor visits (Weekly) 2. Patient's income lost due to hospital visits and their carer's income lost accompanying the patients to routine hospital visits (daily) 3. The carer's costs accompanying the patients to the routine hospital visits (daily) 4.Patient's and care taker's transport cost to private doctors or routine hospital visits (Weekly)	The number of doctor visits during inpatient and outpatient stay for each patient	**Inpatient stay** : Weekly cost at 2 months * total number of weekly doctor visits during inpatient stay *Adjusting income lost & accompany costs: **Inpatient stay**: daily cost at 2 months * number of daily doctor visits during inpatient stay **Outpatient stay:** 4 month to 6 month cost = Weekly (or daily) cost at 6 month * total number of monthly visits during outpatient stay from 4 months to 6 months or until the month the patient dies between month 4 and 6. 7 month to 9 month cost : Weekly (or daily) cost at 9 month * total number of monthly visits during outpatient stay from 7 months to 9 months or until the month the patient dies between month 7 and 9.
6. Medication cost (Weekly) 7. Assistance cost (for family members, friends, helpers, nurses, others) (Weekly) 8. Other expenses (Weekly) 9. Patient's and care taker's food cost (Daily)	The number of weeks	**Inpatient stay** : Weekly cost at 2 month * total number of weeks during inpatient stay **Outpatient stay**: 4 month to 6 month cost = Weekly cost at 6 month * total number of weeks during outpatient stay from 4 months to 6 months or until the month the patient dies between month 4 and 6. 7 month to 9 month cost : Weekly cost at 9 month * total number of weeks during outpatient stay from 7 months to 9 months or until the month the patient dies between month 7 and 9. *For daily food expenses: **Inpatient stay**: (Daily cost at 2 month * 7 days) * number of weeks during

		inpatient stay **Outpatient stay**: 4month to 6 month cost = (Daily cost at 6 month * 7 days) * number of weeks during outpatient stay from 4 months to 6 months or until the month the patient dies between month 4 and 6. 7 month to 9 month cost: (Daily cost at 9 month * 7 days) * number of weeks during outpatient stay from 7 months to 9 months or until the month the patient dies between month 7 and 9.

3.2.3.3 Adjustments for health outcome:

Adjustments were also made to the health-related quality of life data collected in the trial.

Firstly, responses across the 5 different health domains in the EQ5D-3L questionnaire (mobility; self-care; usual activities; pain; and anxiety) were examined. Specifically the proportions of responses at each level of the 5 health domains of the EQ5D at 2 months and 9 months were calculated for each treatment group. Using these responses across the 5 health domains, two sets of EQ5D scores were derived, using the UK tariff and Thailand tariff.

Secondly, quality adjusted life years integrate the patient's EQ5D scores at 2 month and 9 months with patient's survival times during the trial period. QALYs were computed based on the method of area under the curve under 3 different scenarios. Linear changes were assumed between assessments at 2 months and 9 months, and from either of these to death.

EQ5D scores at baseline were not collected; instead they were assumed to be at the worst health state of the EQ5D score for UK tariff (-0.594) and the Thailand tariff

(-0.454). This assumption was considered reasonable, as patients with HIV and TBM were too sick or unconscious at baseline for EQ5D to be collected.

<u>Scenario 1:</u> QALYs were calculated for patients who die anytime between baseline and 2 months.

All patients had baseline EQ5D scores fixed at -0.594 (UK tariff) or -0.454 (Thailand tariff). The EQ5D score is zero for death, and so quality of life for patients who die anytime between baseline and 2 months was calculated by the area of the rectangle as in Figure 3-2. In this case, the participants were assumed in the situation of worse than death until an abrupt death.

Equation 1: QALYs were calculated for patients who die anytime between baseline and 2 months.

$$Area = -0.594 * X1$$

X1= 0 – 2 months (0 - 0.16 years)
Y1=0: EQ5Dscores at time point X1

X1 was the duration of time from baseline to death or loss to follow up, which was conditional to be less than 2 months. Here, X1 is in a range from 0 months to 2 months, expressed as fractions of years.

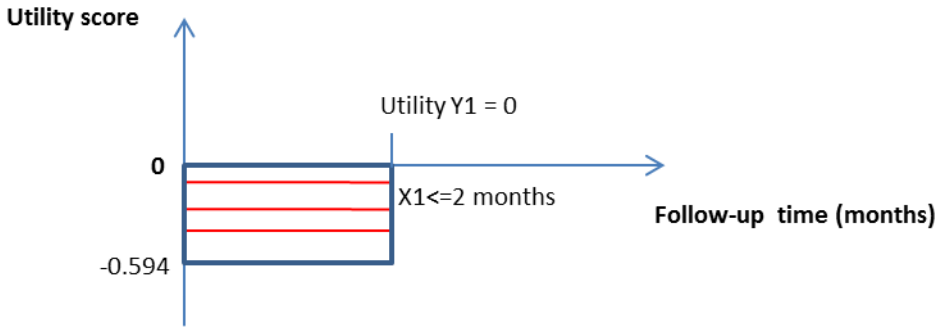


Figure 3-2: Scenario 1 QALYs adjustments

<u>Scenario 2</u>: QALYs calculation for patients who die anytime between 2 months and 9 months

These patients had 3 different EQ5D scores, one at baseline of -0.594, and a EQ5D score at 2 months which represented Y1, and a EQ5D score at death (0) which were defined as Y2. Y1 could be either a positive or a negative EQ5D score, in the range from -0.594 to 1. The EQ5D score at Y2 was set as zero. X1 was fixed at 2 months, and X2 would be any time points from 2 months to 9 months.

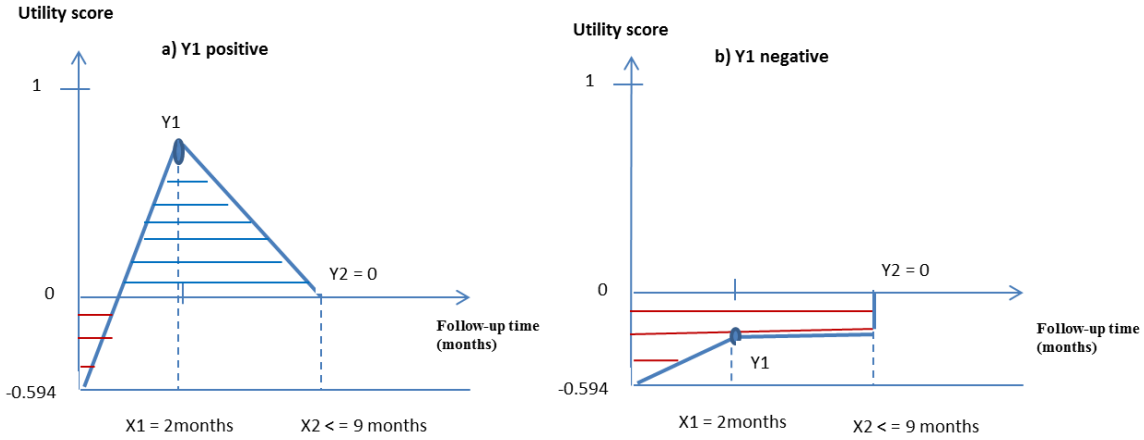


Figure 3-3: Scenario 2 QALYs adjustments

Equation 2: QALYs calculation for patients who die anytime between 2 months and 9 months.

For patients with positive Y1 (Figure 3-3 a) the general formula will be:

$$Area = \frac{(Y_1 + 0.594) * X_1}{2} + \frac{(X_2 - X_1) * (Y_1 + Y_2 + 2 * 0.594)}{2} - (0.594 * X_2)$$

For patients with negative Y1 (Figure 3-3 b) the general formula will be:

$$Area = \frac{(Y_1 + 0.594) * X_1}{2} + (X_2 - X_1) * (Y_1 + 0.594) - (0.594 * X_2)$$

Where:
X1 = 2 months (0.16 years)
X2= 2 months to 9 months (0.16 year to 0.75 year): the time point at which the patient dies.
Y1: Utility scores at 2 months.

For patients with positive Y1 (Figure 3-3a), it was assumed that patient's HRQL improved linearly from baseline to 2 months (Y1) to reflect the fact that neural tissue might have improved slowly and gradually rather than in a stepwise fashion, and then their health got worse and declined gradually from Y1 to Y2 , these patients then die after 2 months. In fact, the progression from baseline to Y1 could be linear, or any other shapes. The true shape would be closely estimated if more follow up points were recorded. No such studies have assessed the changes in health utility scores of HIV/TBM patients during the treatment. The linear recovery for patients after receiving treatment has also been seen in a study that evaluated the patient's HRQL in the critical care [146] and HIV/AIDS patients over time [129].

For patients with negative Y1 (Figure 3-3b), the linear recovery from baseline to 2 months (Y1) was assumed again in this scenario. Patients who were already at the state "worse than death" at 2 months were assumed to stay constant at Y1 then incurred abrupt death. This assumption was made on the grounds of this study [147] which examined the quality of life in 28 adults one year after recovery from bacterial meningitis ($n = 17$ due to *Streptococcus pneumoniae*; $n = 11$ due to *Neisseria meningitides*). Some pneumococcal patients in this study showed cognitive slowness and very low quality of life one year after bacterial meningitis. Another study also showed that meningitis patients were subjected to a very slow recovery in the mental health during the first few months of treatment [148]. Therefore, the HRQL of patients who were already at the state "worse than death" and carried a very severe disease such as HIV-TBM might not improve much from Y1 to Y2 and then they incurred sudden death.

<u>Scenario 3</u>: QALYs calculation for patients alive beyond 9 months follow-up

Patients had three differentEQ5D scores, one at baseline of -0.594, and EQ5D scores at 2 months (Y1) and 9 months (Y2). Y1 and Y2 ranged from -0.594 to 1. Time X1 was fixed at 2 months, time X2 was fixed at 9 months. The EQ5D scores at 9 months (Y2) can be higher or lower than EQ5D score at 2 months (Y1).

Equation 3: QALYs calculation for patients alive beyond 9 months follow-up

$$Area = \frac{(Y_1 + 0.594) * X_1}{2} + \frac{(X_2 - X_1) * (Y_1 + Y_2 + 2 * 0.594)}{2} - (0.594 * X_2)$$

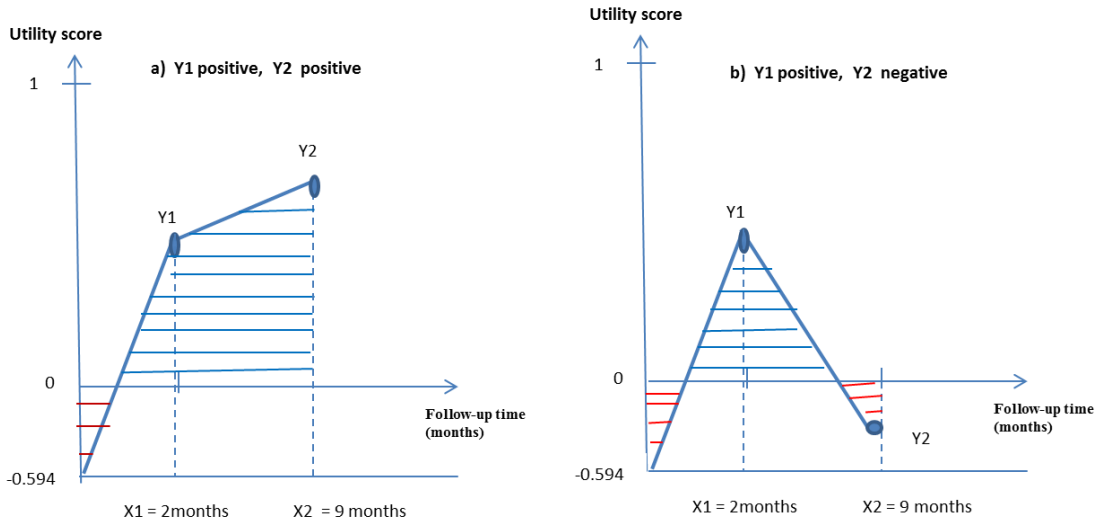
Where:

X1 = 2 months (0.16 year)

X2= 9 months (0.75 year)

Y1: EQ5D scores at 2 months

Y2: EQ5D scores at 9 months



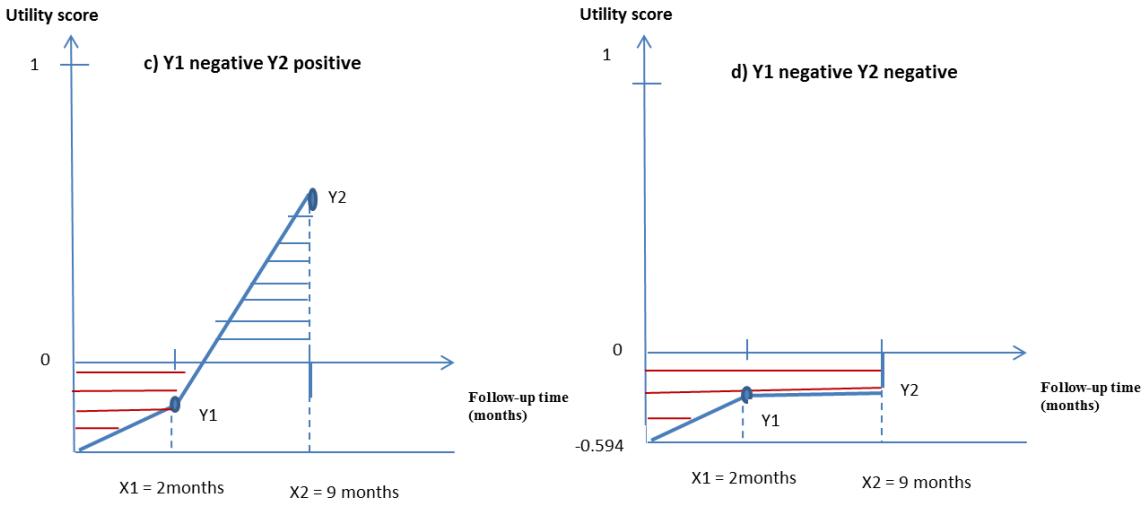


Figure 3-4: Scenario 3 QALYs adjustments

For patients with negative or positive EQ5D scores at Y1 and positive/negative EQ5D scores at Y2 (Figure 3-4a and b), patient's health quality life was assumed to change linearly from baseline to Y2. However, a constant and sudden change from EQ5D score at negative Y1 to negative score at Y2 (Figure 3-4 d) was assumed. This assumption was made to reflect that HIV-TBM patients had slow recovery when they were already at the state "worse than death" as seen in [147,148].

3.2.4 **Data analysis**

3.2.4.1 Non-parametric bootstrapping methods for mean differences in costs and QALYs

Costs

The arithmetic mean for each category of cost and for societal costs (total costs) in each treatment group was calculated. As set out by [149] the arithmetic mean (the average cost) is the important summary statistic for budgetary and social perspectives because it allows decision makers to calculate the total cost of adopting a new therapy. The distribution of costs was also determined to deal with the issue of skewness in cost data.

In the statistical analysis of cost data, the inferences around the mean and mean differences between groups were of central interest. The cost difference in means and the 95% confidence interval around the cost differences in means were then calculated in order to determine whether these differences were likely due to chance. The 95% confidence intervals were determined by the bootstrapping method. The non-parametric bootstrap procedure has the advantage of avoiding parametric assumptions while allowing inferences about arithmetic mean cost [150]. These 1000 bootstrap replicates of mean difference were ranked and 95% confidence intervals were marked at the 25^{th} and 975^{th} ranked points to represent the upper and lower 95% confidence limits. 1000 bootstrap replications were frequently used in the literature to achieve the precise estimate of cost differences [117].

Dealing with censored costs: Kaplan Meier Sample average survival and bootstrapping censored costs

Censoring arises when follow-up information on some study observations is not available for the full duration of interest [151]. In this study, this occurs for two main reasons:

- Patients withdrew from the study and this resulted in incomplete follow-up information.
- Patients had not reached the endpoint of interest - death - by the final date of follow-up and so were administratively censored.

Two common non-parametric interval methods for dealing with censoring in an economic analysis are the Kaplan-Meier sample average (KMSA) estimator and the inverse probability weighting estimator [151–153]. This study considered the KMSA estimator to be an appropriate method because in this approach, the average

societal costs were adjusted directly with the trend of death (survival probability). This helps to deal with the substantial mortality existing in the first 2 months of the study.

The KMSA method adjusted the average societal costs for each of the treatment groups. The KMSA divided the study period into days (275 days). For each day the average societal costs of those patients still alive and not censored at the beginning of that day were estimated. These mean estimates were then weighted by the KMSA estimator, that is, the probability of survival across each day, conditional on having survived the previous day. The survival probability was estimated by the "survival" package in R software. The weighted mean estimates were then summed over 275 days to obtain an estimate of the mean censored adjusted societal costs. The next step was to generate 1000 replicates of mean censored adjusted societal costs based on the bootstrapping method. The 95% confidence intervals around for the difference in mean censored KMSA adjusted societal costs were calculated based on the percentile approach.

Health outcomes

Bootstrapping methods were also employed to generate the 95% confidence intervals around the mean differences in EQ5D score (for UK and Thailand tariffs), VAS at 2 months and 9 months and QALYs. Chi-square test and Mann-Whitney test were used to examine the differences between means and proportions.

3.2.4.2 Incremental cost-effectiveness ratios

The focus of our economic analysis was to estimate the incremental cost-effectiveness ratio, (ICER) which was the ratio of mean difference in costs divided by the mean difference in effects between two treatment groups.

Equation 4: Incremental cost-effectiveness ratios for HIV/TBM project

$$\frac{Cost2 - cost1}{Effect\ 2 - Effect1} = \frac{\Delta C}{\Delta E}$$

Cost2 and cost1 were the arithmetic mean cost in each group, and effect2 and effect1 were the arithmetic mean effect in immediate ART, and deferred ART respectively. The ICER was computed for complete-cases, multiple imputation, KMSA complete-cases, and KMSA imputation analysis.

The 95% confidence intervals for ICERs were computed based on the percentile method. However if the ICER yielded a negative ratio, 95% confidence limits intervals around ICER could not be interpreted as a valid approach to address uncertainty in cost-effectiveness analysis. As negative ratios from negative cost difference and positive effect difference was the same as a ratio from positive cost difference and negative effect difference: that is, two completely different situations would have the same ICERs [150]. As a result, the 95% confidence intervals for the negative ICER could not be informative to differentiate which intervention is cost-effective or not. Two other approaches were adopted to give more plausible interpretations of negative ratios and the economic values of each treatment: cost-effectiveness acceptability curves, and net monetary benefit statistic.

3.2.4.3 The cost-effectiveness acceptability curve: the non-parametric bootstrapping approach

The cost-effectiveness acceptability curves (CEAC) represented the probability that the new intervention was cost–effective for different values of a decision maker's maximum willingness to pay (WTP)[154]. In this study the CEAC was generated based on the non-parametric bootstrapping replications. The WTP values were

assumed to lie somewhere between zero and 22,727 USD/QALY (500 million VND/QALY), and these values were displayed in increments of 10 million VND on the x-axis. This range was examined because it has not been known how much healthcare decision makers are willing to pay for a QALY gained in Vietnam. The y-axis gave the probability that the new intervention – the immediate ART - was likely to be cost effective. The CEAC traced the probability that the immediate ART could be cost-effective as the WTPs varied from zero to 22,727 USD/QALY. The CEAC also gave information about the 95% confidence intervals of the ICER. If the CEAC cut the two horizontal lines at the 0.025 and 0.975 points on the vertical axis, this implied that the 95% confidence limits on the cost-effectiveness exist, and vice versa.

3.2.4.4 Net benefit ratio

The net benefit ratio is defined as follows: The basis of cost-effectiveness decision rule was that a decision maker would consider an intervention acceptable if its ICER was less than their maximum WTP values for a health gain. Suppose π represented the maximum a policymaker was willing to pay; then an intervention was cost-effective when:

$$\frac{\Delta C}{\Delta E} < \pi$$

This above formula could then be rearranged to transform the ratio to a linear expression, known as net monetary benefit (NMB):

$$Net\ monetary\ benefit\ (NMB) = \Delta E\pi - \Delta C$$

Equation 5: The net monetary benefit ratio for HIV/TBM project

The interpretation of NMB was that if the intervention had a NMB greater than zero, this new intervention was cost-effective and should be adopted. If NMB was negative, NMB <0, it was not cost-effective as the costs were greater than the benefit. The advantage of NMB was also that it overcame the problems arising from negative ICERs because there was only one simple interpretation of the NMB statistic: larger NMBs were better and smaller NMBs were worse [150,155].

There were two approaches to calculate the net monetary benefit: the parametric method and non-parametric method.

a/ The net-benefit framework: non-parametric approach:

1000 bootstrap replicates of costs and effect differences were used to calculate the NMB statistic for each of the WTP values zero and 22,727 USD/QALY (50 increments). For each of these WTPs, the summary statistics of NMB statistics (mean, standard error) were obtained. The 95% confidence intervals were computed based on the percentile approach. The non-parametric procedure of calculating NMBs were implemented for 4 scenarios: complete cases, KMSA complete cases, MI analysis, and KMSA MI analysis.

b/ The net-benefit framework: parametric approach

From the non-parametric method, 1000 bootstrapped NMBs were generated and the distribution of these 1000 NMBs were recognized as closer to normal distribution than the ICER based bootstrap. Therefore it was possible to use the normal distribution to calculate the 95% confidence intervals for NMBs as the following formulations. The mean estimation of NMB statistics was then derived in relation to different values of WTP [150]. The 95% confidence intervals for NBMs

that contained zero would be the decision threshold to determine whether immediate ART was net monetarily beneficial with 95% level of confidence.

Equation 6: The Net monetary benefit with 95% confidence intervals

95% NMB CI = NMB $\pm\, t_{\propto/2} SE_{NMB}$

- Calculating standard error for NMB equals to:

  $SE^2_{NMB} = SE^2_{Difference\ in\ costs} + (W^2 + SE^2_{Difference\ in\ QALYs}) -$

  $2\ W\ \rho\ SE_{Diff\ in\ costs} SE_{Diff\ in\ QALYs}$

  $SE_{NMB} = (SE^2_{Difference\ in\ costs} + (W^2 + SE^2_{Difference\ in\ QALYs}) -$

  $2\ W\ \rho\ SE_{Diff\ in\ costs} SE_{Diff\ in\ QALYs})\text{^}0.5$

$\rho\ SE_{Diff\ in\ costs} SE_{Diff\ in\ QALYs}$: Correlation of difference in costs and difference in effects

- Calculating correlation of difference in costs and difference in effects were as followings:

$\rho\ SE_{Diff\ in\ costs} SE_{Diff\ in\ QALYs}$

$$= \frac{\begin{array}{l}(p_{effects\ and\ costs\ for\ \ Immediate\ ART} * SE_{effects\ in\ immediate\ ART} * SE_{costs\ \ in\ immediate\ ART}) + \\ (p_{effects\ and\ costs\ for\ deffered\ ART} * SE_{effects\ in\ deferred\ ART} * SE_{costs\ \ in\ deferred\ \ ART}) +\end{array}}{SE_{diff\ in\ effects} * SE_{diff\ in\ costs}}$$

- Calculating standard error of difference in costs and effects were as followings:

  $SE_{diff\ in\ costs} = (SE_{cost\ \ in\ immediate\ ART})^2 + (SE_{cost\ \ in\ deferred\ ART})\text{^}2$

$SE_{diff\ in\ effects} = (SE_{effect\ in\ immediate\ ART})^2 + (SE_{effect\ in\ deferred\ ART})\text{^}2$

3.2.5 **Sub-group analysis**

Sub-group analysis was conducted to make the results generalizable to populations with employment, urban/rural residence and different severity of disease. The

following sub-groups were used because they were pre-specified in the clinical statistical analysis plan. The reasons for selecting these variables are shown in Table 3-7. To reduce the chance of a type I error, this analysis employed a Bonferroni method to adjust the alpha level to 0.01 (0.05/3 comparisons for each subgroup) [156].

Table 3-7:Variable selection for sub-group analysis and justification for the choice of subgroups.

Subgroups	**Justification for choosing this sub-group**
Patient's residence: People living in HCM city or other provinces	Costs and health utility scores are greatly affected by the patient's residence [109,112,157]
Patients alive at different follow-up time points (2months, 6 months, 9 months)	The difference in utility score was found greatest for those people diagnosed with HIV in earlier calendar periods[158].
Patients with CD4 counts at baseline (≤50 cells/µL, >50 cells/µL)	Lower CD4 counts were associated with higher costs [80,159]
TBM grade 1, 2, 3 at baseline	Our trial found that only the baseline TBM disease grade was strong predictor for death. Furthermore, disease stages were found to be significantly related with costs and health utility scores [95,126,160]

3.2.6 **Scenario analysis**

Base case scenario: The hospital health care costs and the patient health-care costs were analysed as described previously.

Scenario 1: the costs of ARV drugs for both groups in the base case scenario were reduced to make it comparable with the ARV costs in the Duong's study [81]

which was between $257 to $443 (2013 USD). The Vietnamese government procured the drugs at this level of price during the year 2009 to 2013.

Scenario 2: The doctor visits per week at 2 months in the base-case scenario were assumed to increase by 70% in the immediate ART group to reflect significantly more grade 3 or grade 4 adverse events (AEs) during the inpatient stay in this group. Patients on early ART had 35% more grade 3 or 4 AEs in the first 2 months than patients on deferred ART [57]. Here we assumed that a single adverse event resulted in 2 doctor visits in this scenario. Higher doctor visits could be tested in further analysis.

Scenario 3: The weekly assistance cost from the patient's caretakers at 2 months in the immediate ART group was increased by 50%, and then reduced by 10% and 20% at 6 months and 9 months respectively. The weekly assistance costs emphasized more grade 4 adverse events during inpatient stay in the immediate ART group and the gradual changes over time to reflect the patient's recovery.

Scenarios 4: The combination of scenarios 1 & scenario 2

Scenario 5: The combination of scenarios1, 2 & 3

One-way sensitivity analysis was also applied to examine the effect of varying weekly patient health care costs by +/- 25% on the net monetary benefit values at WTP of $2000 per QALY gained.

3.3 **Results**

3.3.1 **Study population of the health economics (EC study)**

EC study recruited a total of 204 patients (101 participants in the immediate ART treatment group and 103 participants in the deferred treatment group).At 2 months

follow-up, nearly half of participants had died and 2 patients had withdrawn in the deferred ART arm. By 6 months, a further 20 percent had died and a further 14 participants had withdrawn, and by 9 months a total of 76 patients remained in the study (36 patients from immediate ART, and 40 patients from deferred ART. The CONSORT flowchart (Figure 3-5 and Table 3-8) gives details of the availability of patients during each time-point in the trial. The immediate ART group was not significantly different from the deferred ART group in terms of the overall rates of withdrawal (5% [5 of 101] and 9% [9 of 103], P >0.05 Chi-square test)

Figure 3-5: The CONSORT flowchart

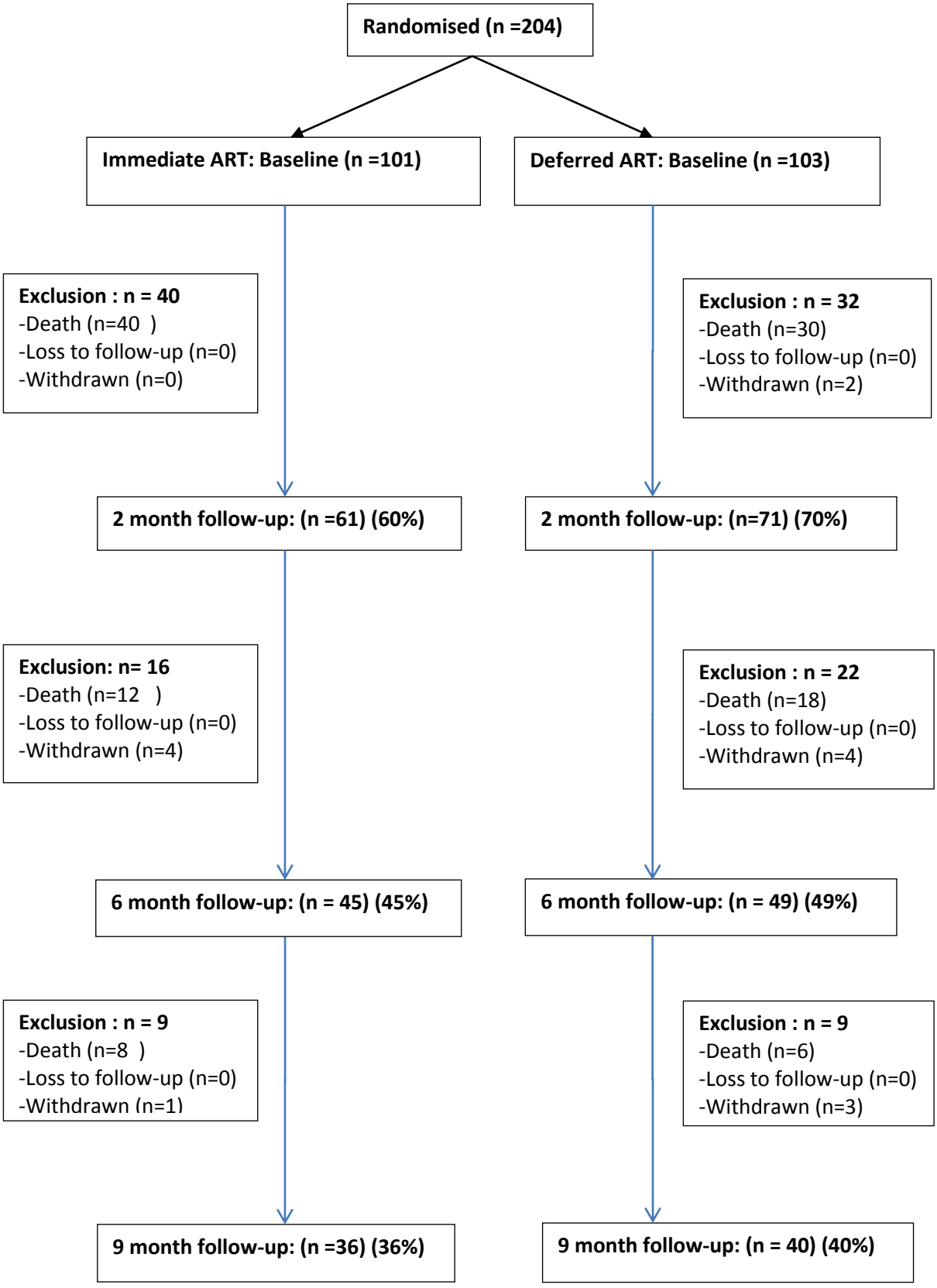


Table 3-8: Number of participants at each follow-up time point

Time points	Immediate ART	Deferred ART	Total
Baseline	101	103	204
2 months	61	71	132
6 months	45	49	94
9 months	36	40	76

3.3.2 **Analysis of missing data**

3.3.2.1 Identifying the proportion of missing costs in patient healthcare costs and visual analog scores

Table 3-9 reports the proportion of missing values for each cost category. For medication costs, in the immediate ART group, there was 1 missing value (2%) at 2 months follow up. For the deferred ART group, there were 2missing values (3%) at the 2-month follow-up. These missing values occurred because the patients could not remember how much they had spent. The complete cases analysis mandated that these 3 missing medication costs were removed from the complete-cases analysis. However, two out of these three subjects had medication costs available at 6 months and 9 months and therefore, when adding these costs at different time points together, the complete-case analysis discarded just one subject. As a result, there were 203 participants available for the complete case analysis. There were no missing values reported in the hospital healthcare costs and productivity losses. Complete case analysis and multiple imputation were employed to address the missing values only for medication costs.

Table 3-9: Proportion of missing values (%) in one-week patient healthcare costs at 2 months, 6 months, 9 months for treatment groups(immediate ART and deferred ART)

Patient healthcare costs (%)	2 months		6 months		9months	
	Immediate ART (n=61)	Deferred ART (n =71)	Immediate ART (n=49)	Deferred ART (n=101)	Immediate ART (n=36)	Deferred ART (n=40)
Exam cost	0	0	0	0	0	0
Medication	2%	3%	0	0	0	0
Other expenses	0	0	0	0	0	0
Food	0	0	0	0	0	0
Transport cost	0	0	0	0	0	0
Accompany	0	0	0	0	0	0
Assistance cost	0	0	0	0	0	0

3.3.2.2 Inspecting the pattern of missing data:

The 3 missing medication costs at 2 months (Table 3-9) and 8 missing VAS at 2 months and 9 months (Table 3-18) were explored to see whether they had any relationship with other baseline and follow-up clinical variables (Appendix 7). According to these results, these missing costs and VAS followed the pattern of missing completely at random (MCAR) and/or missing at random (MAR). The accepted methods to address these missing patterns are the application of complete case analysis and multiple imputation; therefore I performed these analyses.

3.3.3 Adjustment for patient healthcare costs and productivity losses

3.3.3.1 Description of positive costs in patient healthcare costs and productivity losses

Table 3-10 reports the proportion of weekly patient's healthcare costs and productivity losses at 2 months, 6 months and 9 months which were positive for each cost category. From this table it can be seen that the majority of the responses (90%) reported that the patients and caretakers did not incur healthcare costs beyond 2 months, except in the food expenses and accompaniment cost categories.

All patients had to pay for food expenses over time. The medication costs were low and nearly zero across different follow-up assessment points. This was because the majority of medication costs were recorded under the healthcare costs incurred by the hospital such as antiretroviral therapy, and TB and antibiotic medication. In this study, the patients were likely to rely on assistance from others as the proportion of positive assistant costs was relatively high, as seen in Table 3-6 (13% at 9 months, 46% at 2 months).

Table 3-10: Proportion of non -zero costs (costs >0) (%) in patient healthcare costs; and productivity losses 2 months, 6 months and 9 months for treatment groups(immediate ART and deferred ART).

Patient healthcare costs (%)	**2 months**		**6 months**		**9 months**	
	Immediate ART (n=101)	**Deferred ART (n=103)**	**Immediate ART (n=101)**	**Deferred ART (n=103)**	**Immediate ART (n=101)**	**Deferred ART (n=103)**
Exam cost	5	6	4	4	0	0
Medication	7	3	2	6	6	0
Other expenses	31	21	20	10	8	8
Food	100	100	100	98	100	100
Transport cost	21	25	84	84	89	95
Accompany cost	100	96	93	82	94	85
Assistance cost	46	35	36	18	17	13
Productivity losses	28	38	33	24	47	33

3.3.3.2 Description of the average weekly patient healthcare costs and productivity losses at 2 months, 6 months, 9 months

Table 3-11 reports the average weekly patient healthcare costs and productivity losses at 2 months, 6 months and 9 months for the two different treatment groups. Standard deviations were also calculated to accompany the mean values, but there was insufficient space to report them in the table. The costs of examination per week at 2 months and 6 months and 9 months were nearly zero for both of the groups. This reflects the fact that patients did not go to any doctor's clinics outside the scheduled visits recommended by the trial. The patients and their care's givers

in immediate ART were likely to lose 88 cents of their income for waiting and health examination associated with a single hospital visit and $1.04 for those on deferred ART. The differences in these productivity losses were not significant (P=0.3, according to Wilcoxon test). The productivity losses was small in both groups because these costs were associated with a single hospital visit at 2 months, 6 months and 9 months (according to the cost questionnaire).

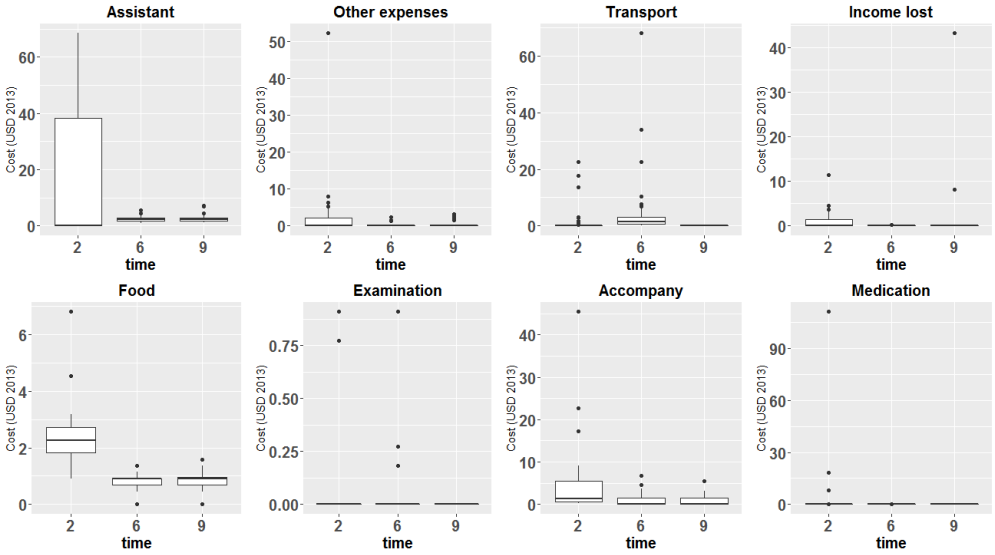
Figure 3-6 depicts the two boxplots that show weekly patient healthcare costs daily productivity losses (income lost) at 2 months, 6 months and 9 months for the immediate ART strategy and the deferred ART strategy. The boxplots show the distribution, the average and the range of the weekly costs. For the deferred ART group, the food expenses and accompaniment costs at 2 months were higher than these costs at other follow-up time points. The other weekly costs had a small fluctuation over different follow-up time points for both of the treatment groups. These graphs reflect the trend of the patient healthcare costs during the 9 month-period, which might not be true especially for the patients in immediate ART group, experienced higher frequency of adverse events during the first 2 months than the deferred ART.

Table 3-11: The average weekly unadjusted healthcare costs incurred by patients, care takers and productivity losses at 2 months, 6 months, and 9 months for different treatment groups (Year 2013 currency: US dollars , 1 USD = 22,000VND)

Patient healthcare costs (US dollars	**2 months**		**6 months**		**9 months**	
	Immediate ART (n=61)	**Deferred ART (n=71)**	**Immediate ART (n=45)**	**Deferred ART (n=49)**	**Immediate ART (n=36)**	**Deferred ART (n=40)**
Exam cost	0.04	0.05	0.02	0.04	0	0
Medication	2.3	0.19	0.01	0.67	1.43	0
Other expenses	1.83	0.6	0.63	0.43	0.09	0.14
Food	3.34	3.33	3.07	3.13	3.54	2.79
Transport cost	1.2	0.6	4.8	3.2	6.2	5.4
Accompany	3.71	2.71	3.59	2.34	4.32	2.81

Assistance cost	15.79	10.6	11.89	5.15	5.04	4.09
Productivity losses	0.88	1.04	0.84	0.5	1.31	0.67

Immediate ART: Boxplot of one-week costs at different follow-up time points



Deferred ART: Boxplot of weekly costs at different follow-up time points

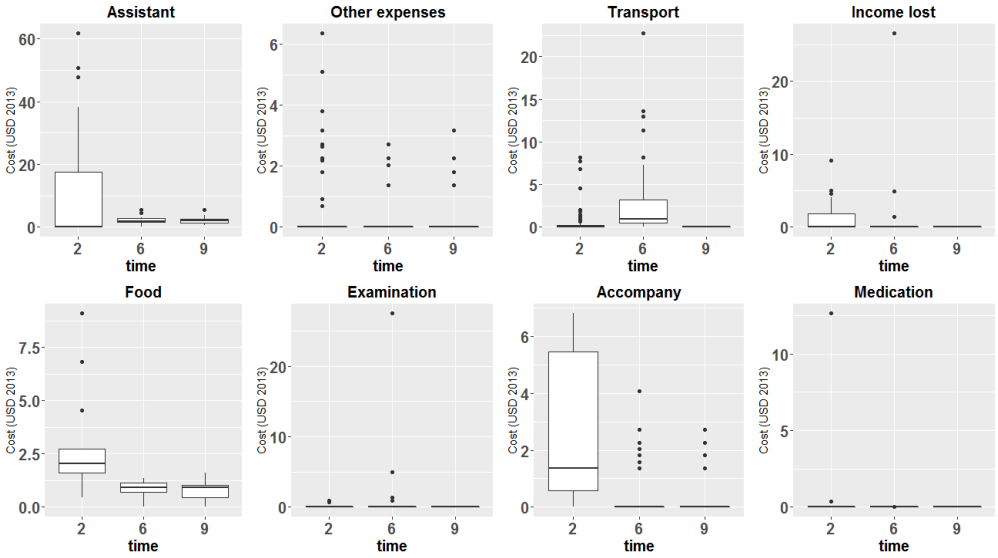


Figure 3-6: The distribution of the weekly patient healthcare costs at 2 months, 6 months, 9 months for immediate ART strategy (top figure) and deferred ART strategy (bottom figure).

3.3.3.3 Two-part models for patient healthcare cost and productivity losses for three different follow-up periods (baseline to 3 months, 4months to 6 months and 7 months to 9 months) and for different treatment groups:

The previous analysis showed that the weekly patient healthcare costs obtained from the questionnaire contained a substantial number of zero values: that is, periods where no costs were incurred. Therefore, two-part models were employed to predict these costs in periods where no data were available. Table 3-12 presents the predicted probability of incurring positive costs, the predicted weekly costs conditional on some cost being incurred, and the unconditional weekly costs at 2 months, 6 months, and 9 months for complete case analysis and in multiple imputation scenarios. The predicted weekly costs were similar to the unconditional weekly costs in both scenarios. Exam costs at 9 months received no responses at all, so these costs were assumed to be zero for this period.

Table 3-12: The predicted probability of obtaining positive costs and the predicted weekly costs conditional on some cost being incurred and the unconditional one-week costs at 2 months, 6 months, and 9 months for complete case analysis and in multiple imputation scenarios (2013 USD)

COMPLETE- CASE			
2 months (n=131)	**Predicted probability (mean-logit)**	**Conditional costs (mean-GLM)**	**Unconditional costs (mean)**
Exam cost	0.056	0.89	0.05
Accompany cost	0.976	3.27	3.21
Transport cost	0.23	4.45	0.9
Productivity losses	0.33	2.71	0.93
Medication	**0.047**	**19.54**	**1.16**
Food expenses	0.879	0.95	0.84
Other expenses	0.252	5.09	1.14
6 months (n=94)	**Predicted probability (mean-logit)**	**Conditional costs (mean-GLM)**	**Unconditional costs (mean)**
Exam cost	0.043	3.58	0.05
Accompany cost	0.87	3.24	2.93
Transport cost	0.84	5	4

MULTIPLE IMPUTATION			
2 months (n=132)	**Predicted Probability (mean-logit)**	**Conditional costs (mean-GLM)**	**Unconditional costs (mean)**
Exam cost	0.053	0.88	0.05
Accompany cost	0.98	3.26	3.2
Transport cost	0.23	4.45	0.9
Productivity losses	0.33	2.71	0.94
Medication	**0.0682**	**14.64**	**1.15**
Food expenses	0.87	0.95	0.84
Other expenses	0.26	4.94	1.14
6 months (n=94)	**Predicted Probability (mean-logit)**	**Conditional costs**	**Unconditional costs (mean)**
Exam cost	0.043	3.58	0.05
Accompany cost	0.87	3.24	2.93
Transport cost	0.84	5	4

Productivity losses	0.287	2.89	0.7
Assistant cost	0.266	34.13	8.74
Medication	0.043	5.84	0.35
Food expenses	0.851	0.9	0.78
Other expenses	0.15	3.63	0.58
9 months (n=76)	**Predicted Probability (mean-logit)**	**Conditional costs (mean-GLM)**	**Unconditional costs (mean)**
Exam cost	0	0	0
Accompany cost	0.89	3.91	3.57
Transport cost	0.91	7.25	6.34
Productivity losses	0.39	2.31	0.98
Assistant cost	0.14	71.11	6.04
Medication	0.03	25.73	0.68
Food expenses	0.88	0.92	0.81
Other expenses	0.08	3.47	0.16

Productivity losses	0.287	2.44	0.7
Assistant cost	0.266	34.13	8.74
Medication	0.043	5.84	0.35
Food expenses	0.851	0.9	0.78
Other expenses	0.15	3.64	0.57
9 months (n=76)	**Predicted Probability (mean-logit)**	**Conditional costs**	**Unconditional costs (mean)**
Exam cost	0	0	0
Accompany cost	0.89	3.91	3.57
Transport cost	0.91	7.25	6.34
Productivity losses	0.395	2.31	0.98
Assistant cost	0.14	71.11	6.04
Medication	0.03	25.73	0.68
Food expenses	0.882	0.92	0.81
Other expenses	0.08	3.47	0.16

3.3.4 **Cost analysis**

3.3.4.1 Cost distribution

Figure 3-7 shows a histogram of the total healthcare costs incurred by hospital, by patients and caregivers, productivity losses and societal costs in complete-case analysis; such histograms were used to assess normality. The distribution of costs was significantly right skewed with a long, heavy, right tail. This could be a result of the presence of a relatively small number of patients with high costs and a large number of patients with lower costs (including zero). Where data were skewed and non-normally distributed, a "typical" cost for a person can best be described by the median. However, the median cannot be used by policy-makers to determine the total cost of treatment for a group of patients. For this reason, I have described the cost data in terms of the arithmetic mean, accompanied by other measures of variability such as standard deviation or interquartile range. These measures are presented in the next part.

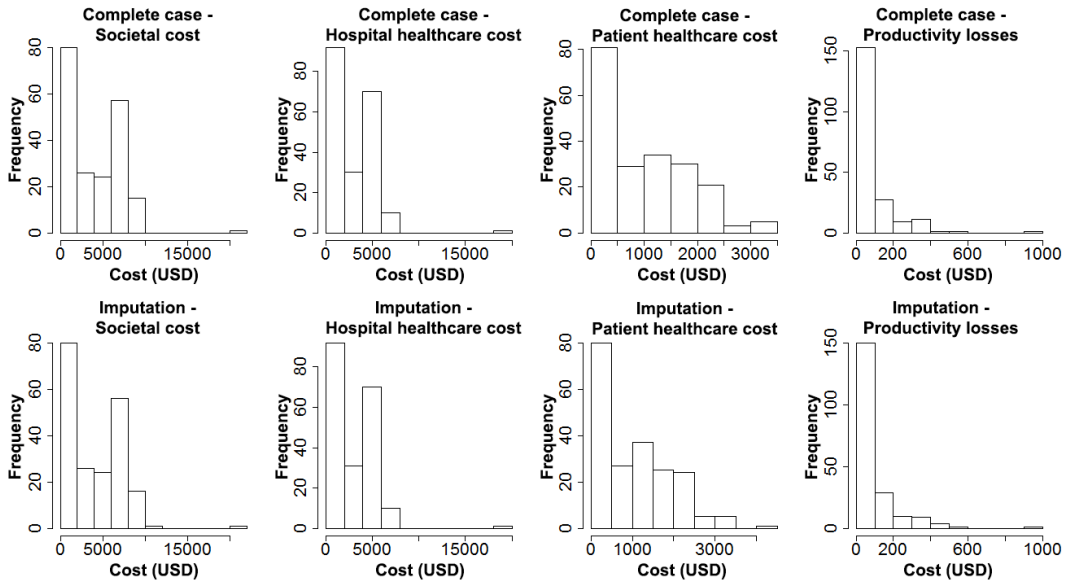


Figure 3-7: Multi histogram for 4 different types of costs: patient healthcare costs, hospital healthcare costs, productivity losses and societal costs during the 9 month

period of the trial. The first and second row represent the complete-case analysis and imputation analysis respectively. Four different histograms correspond to the patient healthcare costs, hospital healthcare costs, productivity losses and societal costs for a study population of 204 participants (complete-cases) and 203 participants (MI analysis) co-infected with HIV/TBM

3.3.4.2 Hospital healthcare costs: mean differences of costs with non-parametric bootstrap methods over the duration of the trial (up to 9 months) by treatment group

The average costs per participant incurred by the hospital for different treatment groups over the 9 month-period of the trial and the mean differences in hospital healthcare costs between treatment groups in both complete – cases (CC) and multiple imputation (MI) scenarios were presented Table 3.13 and Figure 3-8. Over 9 months the hospital spent approximately $3,108 per participant in CC & MI analysis for the immediate ART group and $2,615 to $2,619 per participant in MI and CC analysis for the deferred ART group. There was only value in the immediate ART versus 2 values for the deferred ART as there were no missing data in the immediate ART. The cost for the immediate ART group was higher than for the deferred ART group by an average of $489 to $493 in CC and MI analysis respectively. However the differences in hospital healthcare costs were not significantly different according to percentile bootstrapping approach $489 (95% CI -196 to 1,194 in CC analysis, and$ $493 (95% CI -144 to 1,164 in MI analysis). These average healthcare costs in both treatment groups were twice the average yearly GDP in Vietnam in 2007 (when the trial was conducted), which was $919 [161]. These costs were also substantially higher than the prevailing yearly GDP in 2013 of $1,711 [161]. Figure 3-8 shows proportion of hospital healthcare costs for different treatment groups over 9 months period of the trial both CC and MI analysis. The largest proportion of hospital healthcare costs was the costs of the

antiretroviral drugs (ARVs) which accounted for nearly 80 percent of total costs in both treatment groups. (The cost of ARV drugs was $2,475 for immediate ART in CC analysis versus $1,950 for deferred ART in CC analysis).

When examining the hospital healthcare costs components, the patient's hospital healthcare costs were determined by the patient's treatment periods (days) and the intensity of the resources used during the treatment period. The cost of the antiretroviral drugs (ARVs) in the immediate ART was more expensive than in the deferred ART by an average of $518 (95% CI -87 to 1099 in CC analysis) and $525 (95% CI -69 to 1,106 in MI analysis) because the patients in the immediate ART group took the ARV drugs 2 months earlier than the deferred ART group (Figure 3-8). However, the differences in the costs of ARVs did not achieve the 95% significance test based on percentile bootstrapping approach. Maybe there was insufficient power to achieve this significance test. As the costs of the ARV drugs were the largest item in hospital healthcare costs, the wide differences in ARV costs led to the wide differences in total hospital healthcare costs. In the subsequent analysis I will group the patients with similar survival times, disease severity at baseline (for example: TBM grade) for the repeated evaluation of the differences in costs and the cost-effectiveness (as shown in the sub-group analysis).

Apart from the costs of ARVs, the immediate ART group was similar to the deferred ART group in terms of the expenditures for the TB drugs by -$5 (95% CI -12 to 2, MI analysis), blood tests -$7 (95% CI -22 to 8) microbiological diagnostic tests $2 (95% CI-13 to 9), serological tests -$10 (95% CI -24 to 5), CD4 count tests -$6 (95% CI -14 to 2), bed costs -$5 (95% CI -42 to 33), and care-fee -$2 (95% CI -5 to 1).

These non-significant differences in costs were explained by 2 reasons. Firstly, significantly more patients in the immediate ART group experienced grade 4 adverse events (102 vs 87 in the immediate ART and deferred ART groups, p=0.04). Therefore these patients might have consumed more healthcare resources during their treatment period such as antibiotic, other medicines, and blood transfusions (anemia was a recognized side effect of the antiretroviral drug AZT). However, the more intensive resources use within 9 months was offset by the slightly shorter treatment days caused by higher mortality in the immediate ART group. Nevertheless the difference in treatment days between two groups was not so profound (145 vs 160 treatment days in the immediate ART and the deferred ART, difference: -16 treatment days 95% bootstrapped CI -50 to 18), therefore the differences in hospital healthcare costs were not sufficiently large to fulfill the 95% significance test.

Table 3-13: Average hospital healthcare costs per participant over the duration of the trial (up to 9 months) by treatment group and the differences in hospital healthcare costs between treatment groups in complete case and imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND)

Hospital healthcare costs	Immediate ART		Deferred ART		Differences in costs (Immediate ART – Deferred ART)	
	Complete-cases (n=101) Mean (SD)	Imputation (n=101) Mean (SD)	Complete-cases (n=102) Mean (SD)	Imputation (n=103) Mean (SD)	Complete-cases Mean (95% CI)	Imputation Mean (95% CI)
ARVs	2475 (2505)	2475 (2505)	1957 (1825)	1950 (1818)	518 (-87 1099)	525 (-69 1106)
TBs	21 (26)	21 (26)	26 (27)	26 (27)	-5 (-12 2)	-5 (-12 3)
Antibiotic	34 (90)	34 (90)	23 (79)	23 (78)	11 (-11 33)	11 (-12 33)
Other medicines	65 (77)	65 (77)	54 (57)	54 (57)	11 (-8 30)	11 (-7 29)
Blood test	76 (52)	76 (52)	83 (54)	83 (54)	-7 (-22 8)	-7 (-22 7)
Microbiological diagnostic tests	68 (47)	68 (47)	70 (39)	70 (39)	-2 (-13 9)	-2 (-13 10)
Serological tests	79 (48)	79 (48)	89 (56)	89 (56)	-10 (-24 5)	-10 (-24 4)
CD4 count tests	45 (28)	45 (28)	51 (30)	51 (30)	-6 (-14 2)	-6 (-14 1)
Diagnosis costs	69 (111)	69 (111)	85 (123)	85 (123)	-16 (-49 15)	-16 (-48 16)
Administration costs	4 (10)	4 (10)	2 (2)	2 (2)	2 (-0.2 4)	2 (-0.1 4)
Bed costs	109 (143)	109 (143)	114 (129)	116 (130)	-5 (-42 33)	-7 (-44 31)
Procedures	9 (11)	9 (11)	10 (13)	10 (13)	-1 (-4 3)	-1 (-4 3)
Device	17 (20)	17 (20)	18 (20)	18 (20)	-1 (-7 5)	-1 (-6 5)
Blood transfusion	8 (19)	8 (19)	4 (12)	4 (12)	4 (-0.1 9)	4 (0.2 9)
Oxygen	7 (18)	7 (18)	4 (13)	4 (13)	3 (-2 7)	3 (-2 7)
Food expenses	17 (42)	17 (42)	20 (52)	21 (52)	-4 (-17 7)	-4 (-17 8)

Hospital healthcare costs	Immediate ART				Deferred ART				Differences in costs (Immediate ART – Deferred ART)					
	Complete-cases (n=101) Mean (SD)		Imputation (n=101) Mean (SD)		Complete-cases (n=102) Mean (SD)		Imputation (n=103) Mean (SD)		Complete-cases Mean (95% CI)			Imputation Mean (95% CI)		
Care fee	6	(11)	6	(11)	8	(11)	8	(11)	-2	(-5	0.9)	-2	(-5	1)
Other medical expenses	0.2	(7)	0.2	(0.8)	0.2	(0.5)	0.2	(0.5)	0.1	(-0.1	0.3)	0.1	(-0.1	0.3)
Total hospital healthcare costs	**3108**	**(2790)**	**3108**	**(2790)**	**2619**	**(2092)**	**2615**	**(2082)**	**489**	**(-196**	**1194)**	**493**	**(-144**	**1164)**

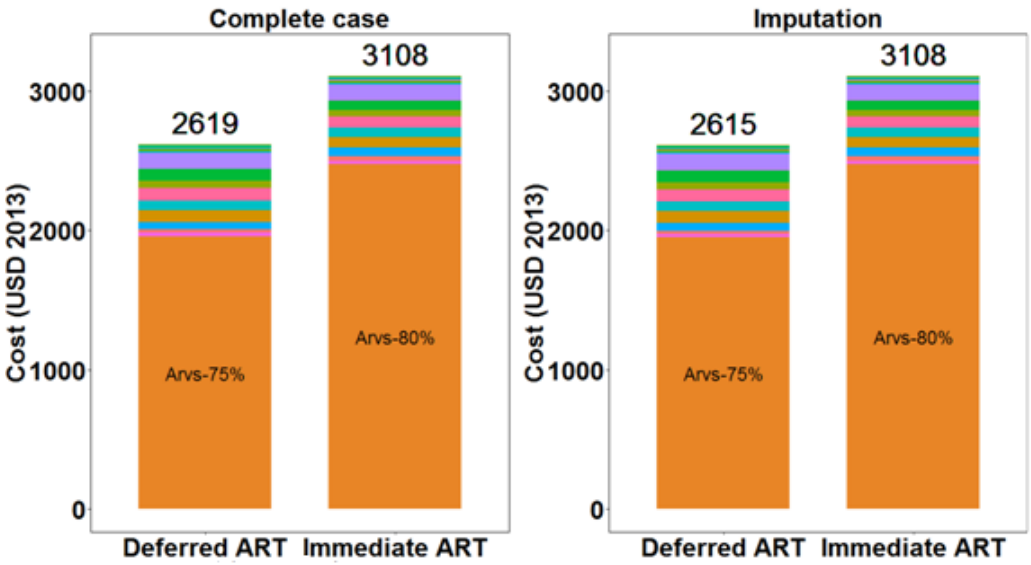


Figure 3-8: The proportion of hospital healthcare costs (%) for different treatment groups over the 9 month period of the trial in complete cases and imputation analysis. The costs are in 2013 US dollars. The *y*-axis shows the mean total hospital healthcare costs per participant during the 9 month period. The x-axis presents the 2 strategies that are being compared: the immediate ART group and the deferred ART group. The costs of ARVs were the main component.

3.3.4.3 Patient healthcare costs: mean differences of costs with non-parametric bootstrapping methods over the duration of the trial (up to 9 months) by treatment groups

The average patient healthcare costs per participant for each treatment group during 9 months for CC and MI analysis were shown in Table 3-14 and Figure 3-9. Over 9 months the total patient healthcare costs were $899 (CC) to $920 (MI) per participant for the immediate ART group and $1000 (CC) to $1062 (MI) per participant for the deferred ART strategy. The immediate ART was not much different from the deferred ART by $101 (95% CI -395 to 188 in CC analysis) to $142 (95% CI -439 to 166 in MI analysis).Regardless of different types of analysis, the cost differences were not statistically significant as the 95% bootstrapping CI intervals cross zero so profoundly.

Examining the components of the patient health care costs, the immediate ART group incurred significantly lower examination costs per patient -$0.7 (95% CI -0.6 to -0.30 in MI analysis) as the 95 % CI intervals did not include zero meaning that the two treatment groups were statistically significant different at the 0.05 level. Lower costs in the immediate ART were also seen in the care costs when accompanying patients to the examination visits -$131 (95% CI -215 to -49 in MI analysis) during the 9-month period. There were two possible explanations. Firstly, the patients in the immediate ART group experienced more severe adverse events during the treatment period therefore they felt sicker and less mobile leading them to make fewer trips to hospital and clinics apart from the routine visits that were predetermined by the clinical trial. Secondly, the patients in the immediate ART group experienced higher mortality rate than the deferred ART eventhough the difference in the mortality did not achieve the 95% significant test in the clinical trial. This led to the fact that the patients in the immediate ART strategy endured slightly shorter treatment days. These two effects reduced the number of health visits to hospital or clinics that led to lower patient's examination costs and the costs of accompanying patients by their carers for the immediate ART group. Slightly higher mortality rate and adverse events in the immediate ART group were also the main reason for higher medication costs per patient in this group at $20 (95% CI 10 to 36) in MI analysis.

Figure 3-9 shows that food costs (40%) were a main contributor to the patient costs, followed by the costs of accompanying patients by the carers to the health visits (30%) and assistance costs (20%). The differences between results using imputation and CC analysis were likely due to missing values in medications.

Over the 9 month period of the study, transport costs were low and examination costs were nearly zero in both treatment groups. These low values could be due to two reasons: (1) over 9 months the patients genuinely did not spend a great deal of money on out of pocket costs, as was illustrated by the many zeros. (2) The costs were estimated from a one-week sampling period immediately before the 2 month, the 6 month and 9 month follow up visits based on two-part model. The exam costs and transport costs at 9 month were all zero so they could not be estimated from the two-part models. Therefore, for these costs, if the patient reported no costs for that week, they were attributed no costs during their outpatient period from 6 months to 9 months, whereas patients who did report costs during that week were attributed these costs monthly over the same period. This approach should result in a reasonable approximation to mean costs across all patients over the periods of interest, but also generates an artificial and extremely unlikely distribution of costs at the patient level. This was the main limitation of the sampling approach and the cost adjustment.

Turning to productivity losses, the results in both complete cases and imputation analysis were aligned with each other. The costs for patients in the immediate ART group were on average $41 (CC) and $42 per participant (MI), slightly cheaper than in deferred ART $122 (CC) and $115 (MI). Therefore, patients and their caregivers in the deferred ART group were likely to lose more income for waiting or examination or when accompanying patients to trial visits. The mean difference of -$81 (CC) and -$73 (MI) was statistically significant at the 95% confidence level (95% CI -114 to -40 in CC analysis and 95%CI -119 to -46 in MI analysis). The immediate ART group incurred lower income lost because these patients experienced more severe adverse events and higher mortality rate. This reduced the

number of times that the patients went to visit hospitals and therefore, they are less likely to be entitled to income lost. Nevertheless, neither the patients nor the caregivers in both of the groups were likely to experience high income lost for waiting or examination or when accompanying patients to trial visits over the 9 month-period. These low costs could be the result of the sampling and cost adjustment method, but was likely to be true in practice as many patients with HIV and TBM felt sick at all times and so may not have been in paid employment in the first place.

Table 3-14:Patient healthcare costs per participant over the duration of the trial (up to 9 months) by treatment group and the differences in patient healthcare costs between treatment groups in complete case and imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND)

Patient healthcare costs	Immediate ART		Deferred ART		Differences in costs (Immediate ART – Deferred ART)	
	Complete-cases (n=101) Mean (SD)	Imputation (n=101) Mean (SD)	Complete-cases (n=102) Mean (SD)	Imputation (n=103) Mean (SD)	Complete-cases Mean (95% CI)	Imputation Mean (95% CI)
Examination costs	0.3 (0.4)	0.3 (0.4)	1 (1)	1 (1)	-0.7 (-0.6 -0.3)	-0.7 (-0.6 -0.3)
Accompany costs	175 (193)	190 (195)	294 (302)	321 (306)	-119 (-202 -42)	-131 (-215 -49)
Transport costs	22 (45)	23 (45)	19 (25)	19 (25)	3 (-7 18)	4 (-7 17)
Assistance costs	239 (277)	241 (280)	208 (269)	214 (270)	31 (-53 125)	27 (-58 114)
Medication costs	24 (61)	24 (61)	4 (4)	4 (4)	20 (10 36)	20 (10 36)
Other expenses	18 (19)	18 (19)	11 (10)	11 (10)	7 (1 11)	7 (1 11)
Food costs	421 (459)	425 (465)	462 (493)	492 548	-41 (-193 107)	-67 (-237 89)
Total patient healthcare costs	**899 (865)**	**920 (882)**	**1000 (918)**	**1062 (996)**	**-101 (-395 188)**	**-142 (-439 166)**
Productivity losses	**41 (54)**	**42 (55)**	**122 (157)**	**115 (153)**	**-81 (-114 -40)**	**-73 (-119 -46)**

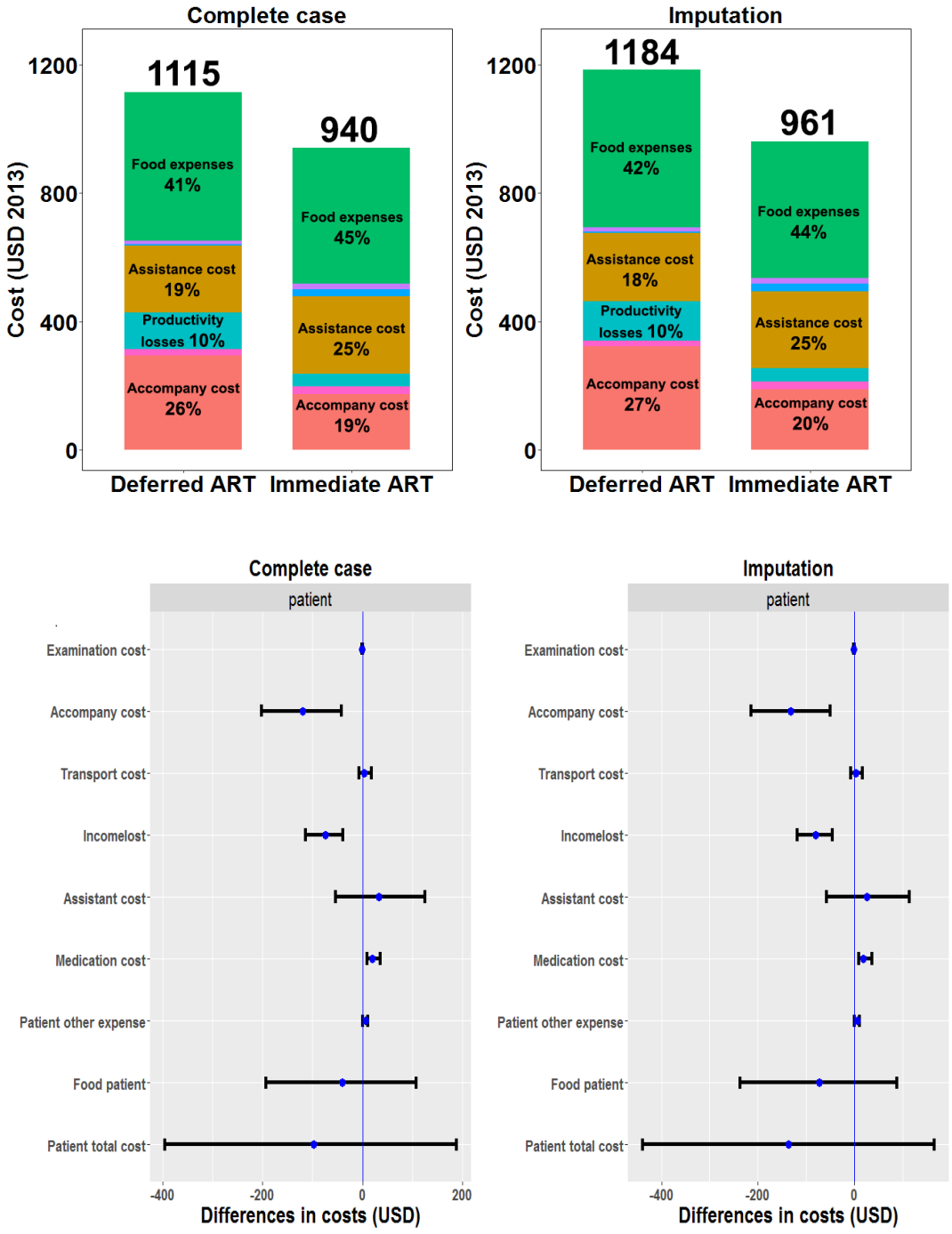


Figure 3-9: The first graph shows the proportion of total patient healthcare costs and productivity losses (%) for treatment groups over 9 months period of the trial – complete cases and imputation analysis. The costs are in 2013 US dollars. The *y*-axis shows the mean total patient healthcare costs per participant during the 9-month period The x-axis presents the 2 strategies that are being compared: the immediate ART group and the deferred ART group. The second graph shows mean difference and 95% confidence intervals of total patient healthcare costs by cost category in complete case and imputation analysis. The dots show estimates of

mean differences in costs of the immediate ART group versus the deferred ART group from 1000 bootstrapped replicates. The error bars represent the 95% confidence intervals of the mean. The blue line represents the mean difference of hospital healthcare when they were negligible. The dots lie on the left-hand side of the line indicate immediate ART group was cheaper than the deferred ART and vice versa.

3.3.4.4 Societal costs: mean differences of costs with non-parametric bootstrapping methods over the duration of the trial (up to 9 months) by treatment group

Societal costs for the two treatment groups over the duration of the trial (9 months) are reported in Table 3-15: these include hospital, patient healthcare costs and productivity losses. The immediate ART group was more expensive than deferred ART group as a treatment strategy for HIV/TBM in terms of societal costs, at $4,049 versus $3,734 (CC) to $4,070 versus $3,799 (MI).However, these cost differences of $315(CC) and $271 (MI) were not statistically significant (95% CI -763to 1,456in CC analysis and -662to 1,358 in MI analysis)**.** Figure 3-11 presents the proportional distribution of societal costs for the two treatment groups. The structure of costs was similar in both groups, with hospital healthcare costs accounting for the largest part of the total cost (80%), followed by the patient healthcare costs (approximately 20%)

Adjusted societal costs with mortality: KMSA approach adjusting mean costs for the trend of survival probability in each treatment group

In this study, there were 36 participants in the immediate ART strategy and 40 participants in deferred ART strategy who were alive at the end of the 9 months period. Furthermore, 5 participants (immediate ART) and 9 participants (deferred ART) dropped out of the trials. These 90 cases were considered as censored cases. After adjusting for censoring, the societal costs for immediate ART and deferred

ART were slightly higher at $4,223 and $3,984 (CC) and $4,273 and $4,065 (MI). Table 3-15 and Figure 3-10 show that the KMSA approach confirmed the findings that the immediate ART group was non-significantly more expensive than deferred ART by $239 (CC) and $208 (MI) (95% CI -775 to 1,352 and 95% CI -819 to 1277 in KMSA CC and MI analysis respectively).

Table 3-15: Societal costs per participant over the duration of the trial (up to 9 months) by treatment group and the differences in societal costs between treatment groups in complete case and imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND)

Societal costs	**Immediate ART Mean (SD)**		**Deferred ART Mean (SD)**		**Differences in costs (Immediate ART – deferred ART) Mean (95%CI)**		
Societal costs (Complete-cases analysis)	4,049	(3571)	3,734	(2990)	315	(-763	1456)
Societal costs (Imputation)	4,070	(3583)	3,799	(3062)	271	(-662	1358)
Societal costs KMSA (Complete-cases)	4,223	(357)	3,984	(301)	239	(-775	1352)
Societal costs KMSA (Imputation)	4,273	(353)	4,065	(308)	208	(-819	1277)

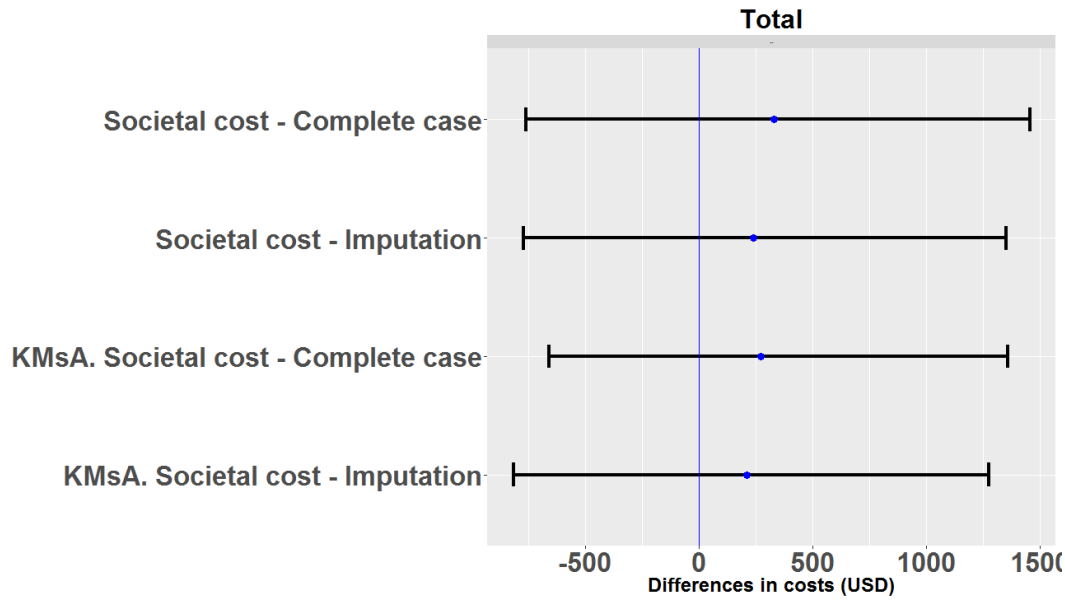


Figure 3-10: Mean difference and 95% confidence intervals of societal costs and adjusted censored societal costs with the KMSA in complete case and imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND**)** .The dots show estimates of mean differences in costs of the immediate ART group versus the deferred ART group from 1000 bootstrapped replicates. The error bars represent the 95% confidence intervals of the mean. The blue line represents the mean difference of societal costs when they were negligible. The dots lie on the left-hand side of the line indicate immediate ART group was cheaper than the deferred ART and vice versa.

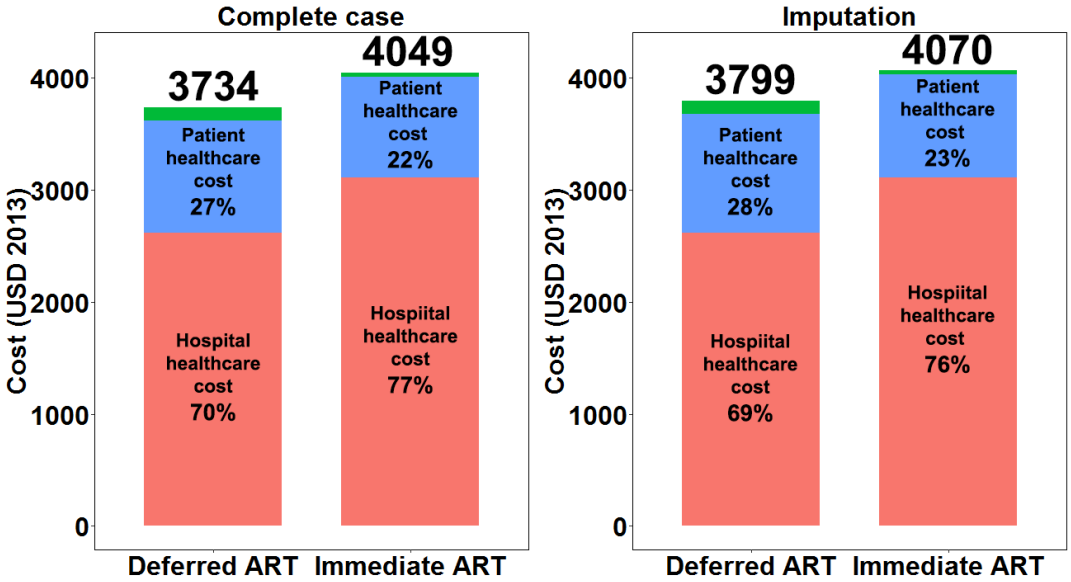


Figure 3-11: The proportion of societal cost for treatment groups over 9 month-period of the trial (%) –complete cases and imputation analysis. The costs are in 2013 US dollars. The *y*-axis shows the mean societal costs per participant during

the 9-month period . The x-axis presents the 2 strategies that are being compared: the immediate ART group and the deferred ART group.

3.3.5 **Health outcomes analysis**

3.3.5.1 Analysis of health states and treatment types

Patient's responses to each of the five different questions contained in the EQ5D questionnaire are reported in Table 3-16, which gives the number and percent of patients at each severity level at 2 months. There was approximately 70 patients incurred death by this time. Surprisingly, more than 50 percent of patients reported experiencing "no problems" in the first 2 months in four of the five questions. This is the time at which patients are assumed to be in a poor health state, as they were supposed to stay in hospital and get treated. However, this pattern of responses was not seen in the "pain" question, where more patients reported having experienced some pain at 2 months. Pain could be linked to adverse events that the patients experienced. In addition, it can be seen that there were more "no problems" responses in deferred ART group than in the immediate ART group across all 5 questions. However, the p-values were greater than 0.05 which supported the null hypothesis that the number of patients in different level of health states was not significantly different by treatment group.

Table 3-17 shows the number of patients in different categories of severity for each EQ5D question at 9 months. Patients in the deferred ART group generally recovered better than immediate ART group across different health states at different level of severity. The p-values of 0.03 from Pearson's Chi test indicates that in the Mobility question the differences between treatment groups were significant at $P<0.05$. Patients in deferred ART group had fewer mobility problems than patients in immediate ART group at 9 months follow-up. However, if taking

account of Bonferroni multiple testing for 5 different health states at 9 months, the significant p-value of mobility was adjusted from 0.03 to 0.15 indicating that there were no differences between 2 treatment groups in mobility.

Table 3-16: EQ5D Health states and treatment types at 2 months follow-up time point

At 2 months EQ5D health states	Immediate ART (n = 61)		Deferred ART (n= 71)		Difference (Immediate ART – deferred ART)		P-values (Chi-square test)
	N	%	N	%	N	%	
Mobility							0.38
No problems	34	56%	48	68%	-14	-12%	
Have problems	10	16%	9	13%	1	4%	
Severe problems	17	28%	14	20%	3	8%	
Self care							0.44
No problems	35	57%	46	65%	-11	-7%	
Have problems	8	13%	11	15%	-3	-2%	
Severe problems	18	30%	14	20%	4	10%	
Usual activities							0.2
No problems	35	57%	46	65%	-11	-7%	
Have problems	6	10%	11	15%	-5	-6%	
Severe problems	20	33%	14	20%	6	13%	
Pain/discomfort							0.41
No problems	22	36%	32	45%	-10	-9%	
Have problems	29	48%	32	45%	-3	2%	
Severe problems	10	16%	7	10%	3	7%	
Anxiety/depression							0.24
No problems	47	77%	51	72%	-4	5%	
Have problems	6	10%	14	20%	-8	-10%	
Severe problems	8	13%	6	8%	2	5%	

Table 3-17: EQ5D Health states and treatment types at 9 months follow-up time point

At 9 months EQ5D health states	Immediate ART (n = 36)		Deferred ART (n= 40)		Differences (Immediate ART – deferred ART)	P-values (Chi-square test)
	N	%	N	%		
Mobility						0.03
No problems	26	72%	35	88%	-9	
Have problems	6	17%	0	0%	6	
Severe problems	4	11%	5	13%	-1	
Self care						0.13
No problems	28	78%	35	88%	-7	
Have problems	4	11%	0	0%	4	
Severe problems	4	11%	5	13%	-1	
Usual activities						0.12
No problems	28	78%	35	88%	-7	
Have problems	4	11%	0	0%	4	
Severe problems	4	11%	5	13%	-1	
Pain/discomfort						0.73
No problems	32	89%	33	83%	-1	
Have problems	4	11%	6	15%	-2	
Severe problems	0	0%	1	3%	-1	
Anxiety/depression						0.82
No problems	32	89%	37	93%	-5	
Have problems	3	8%	2	5%	1	
Severe problems	1	3%	1	3%	0	

3.3.5.2 Analysis of EQ5D scores and visual analogue scores at 2 months and 9 months

For each patient, responses to the five questions were converted to EQ5D scores based on the UK tariff and the Thailand Tariff. The mean differences in EQ5D scores for the two treatment groups at 2 months and 9 months were investigated based on the bootstrapping method. Table 3-18 shows that patients in deferred ART felt slightly better than patients in immediate ART at 2 months and 9 months. The UK tariff and Thailand tariff yielded similar results. The p-values from

bootstrapping methods indicated that there were no statistically significant differences between the 2 treatment groups in terms of EQ5D scores at 2 months (-0.123 95% CI -0.31 to 0.06 UK tariff, -0.104 95% CI -0.27 to 0.077 Thailand tariff) and at 9 months (-0.008 95%CI -0.164 to 0.154 UK tariff -0.032 95% CI -0.203 to 0.135 Thailand tariff). After 9 months of treatment, the EQ5D scores increased from 0.5 at 2 months (meaning that the patients with HIV/TBM had half the quality of life of someone in full health) to 0.8 at 9 months, reflecting the patient's recovery after receiving the HIV and TB treatment.

Turning to visual analogue scores (EQ-VAS) at 2 months there were 6 missing EQ-VAS values (2 missing values for immediate ART and 4 missing values for deferred ART). At 9 months there were 2 missing VAS values from the immediate ART arm, and no missing values from the deferred ART arm. Visual analogue scores at 2 month and at 9 months confirmed the findings from EQ5D scores that patients in deferred ART felt slightly better than immediate ART in CC and MI analysis. However, unlike the EQ5D score at 2 months, the mean difference in VAS score was statistically significant at $p<0.05$ (-4.78 95%CI -8.73 to -0.278): that is, patients in deferred ART felt significantly better than immediate ART at the 2 months follow-up time point. However, for imputation analysis the difference in VAS at 2 months was not statistically significant (-4.05 95%CI -7.98 to 0.32). This is an expected result as the patients in the immediate ART group experienced more adverse severe grade 4 than the deferred ART group during the first 2 months.

Table 3-18: Analysis of EQ5D scores and VAS at 2 months and 9 months follow-up visits and the number of missing values of VAS at 2 months and 9 months

	Immediate ART		Deferred ART		Differences (Immediate ART – deferred ART)	
EQ5D scores (UK tariff)	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**95%CI**
2 months	0.49 (0.58)	61	0.61 (0.5)	71	-0.123(0.094)	(-0.31 0.06)
9 months	0.82 (0.36)	36	0.83 (0.38)	40	-0.008 (0.08)	(-0.164 0.154)
EQ5D scores (Thailand tariff)						
2 months	0.46 (0.55)	61	0.56 (0.48)	71	-0.104 (0.09)	(-0.27 0.077)
9 months	0.78 (0.40)	36	0.81 (0.42)	40	-0.032(0.088)	(-0.203 0.135)
Visual Analog score (CC)						
2 months	64.59 (12.81)	59	69.37(11.23)	67	-4.78(2.095)	(-8.73 -0.278)
9 months	88.2 (8.90)	34	89 (7.12)	40	-0.8 (1.89)	(-4.55 2.85)
Visual analog score (Imputation)						
2 months	64.1 (12.87)	61	68.2(12.0)	71	-4.05 (2.16)	(-7.98 0.32)
9 months	87.64 (9.4)	36	88.4(7.98)	40	-0.77(1.94)	(-4.422 3.23)
Missing Visual Analog values	**n (%)**	**N**	**n (%)**	**N**		
2 months	2 (3%)	61	4 (6%)	71		
9 months	2 (6%)	36	0	40		

3.3.5.3 Analysis of quality adjusted life years for both treatment groups up to the period of the trial

Each patient's EQ5D score was combined with their survival days to generate QALYs based on the arithmetic area under the curve method. Table 3-19 presents the results, showing that QALYs were similar for both CC and MI analysis and for different tariffs. The mean difference in quality adjusted life years (QALYs) was -0.04 QALY (95% CI-0.11 to 0.031 Thailand tariff in MI analysis), indicating that immediate ART was slightly less effective than deferred ART. At P<0.05 there was not a statistically significant difference in quality adjusted life years between both

groups -0.041 QALY (95%CI -0.114 to 0.027 UK tariff in CC analysis) and -0.041 QALY (95% CI -0.114 to 0.029 Thai tariff in CC analysis). Over the 9 months, patients in immediate ART accumulated 0.16 QALYs (1.92 quality adjusted life months) and patients in deferred ART accumulated 0.2 QALYs (2.52 quality adjusted life months) based on the UK tariff and Thailand tariff respectively.

Table 3-19: Average quality adjusted life years over the duration of the trial (up to 9 months) by treatment group -Complete case analysis and imputation analysis

QALYs	**Immediate ART**	**Deferred ART**	**Differences in QALYs (Immediate ART – deferred ART)**
Complete-cases	**Mean (SD)**	**Mean (SD)**	**Mean (95% CIs)**
QALY (UK tariff)	0.168 (0.256)	0.209 (0.277)	-0.041 (-0.11 0.027)
QALY (Thai tariff)	0.162 (0.254)	0.203(0.274)	-0.041 (-0.11 0.029)
Imputation			
QALY (UK tariff)	0.168 (0.256)	0.207 (0.276)	-0.041 (-0.11 0.031)
QALY (Thai tariff)	0.162 (0.254)	0.202 (0.273)	-0.041 (-0.11 0.031)

3.3.6 **Incremental cost effectiveness ratio:**

3.3.6.1 Calculating incremental cost effectiveness ratios: non-parametric bootstrap approach

The statistic of interest in the economic evaluation of health care interventions is the incremental cost effectiveness ratio (ICER), which is defined as the difference in costs over the difference in effects. As QALYs calculated using the UK and the Thai tariff were similar, the Thailand tariff was selected as the main illustrator for the following analysis. Table 3-20 shows that the point estimate of the ICER ratio was a negative ratio of -$7,500 per QALY gained for Thailand tariff in CC analysis and -$6,775 in imputation analysis, -$5,975 for KMSA complete-cases analysis, and -$5,200 for KMSA imputation.

These findings suggest that the immediate ART strategy is a more costly and less effective strategy. Therefore, the deferred ART strategy should be maintained as a standard strategy to treat HIV/TBM patients. However, as the differences in costs and QALYs were deemed insignificant, further methods such as acceptability curve analysis and net monetary benefit analysis were employed to examine the results of 1000 bootstrapped replicates.

Table 3-20: Incremental cost effectiveness computation for Thailand tariff for complete cases and imputation analysis, KMSA complete-cases and KMSA imputation

ICER results	Mean bootstrap cost differences (USD)	Mean bootstrap QALYs Differences	ICER (USD/QALY)
Complete-cases	315	-0.042	-7,500
Imputation	271	-0.04	-6,775
KMSA complete-cases	239	-0.04	-5,975
KMSA imputation	208	-0.04	-5,200

3.3.6.2 95 percent bootstrapped confidence intervals for ICERs: non-parametric bootstrap approach

Figure 3-12 reports the 1000 bootstrap ICER replicates. The red diagonal line indicates the WTP thresholds based on per capita gross domestic product (GDP) in Vietnam in 2013, which was approximately $2000. Most of the bootstrapped replicates lie in the north-west quadrant (quadrant 2) indicating a high probability that immediate ART is less effective and more costly than deferred ART. As for KMSA adjusted censored costs in the CC and MI analysis, 95% confidence intervals of the ICERs were undefined because the bootstrap ICER replicates were scattered into 4 quadrants. As a result, it was impossible to determine the 95% confidence intervals. However, the 95 percent confidence intervals around the ICERs could not differentiate between the negative ICERs for interventions with

more costly and less effective, or more effective and less costly. Therefore, the net monetary benefit analysis and acceptability curves were employed to overcome these problems with negative ratios.

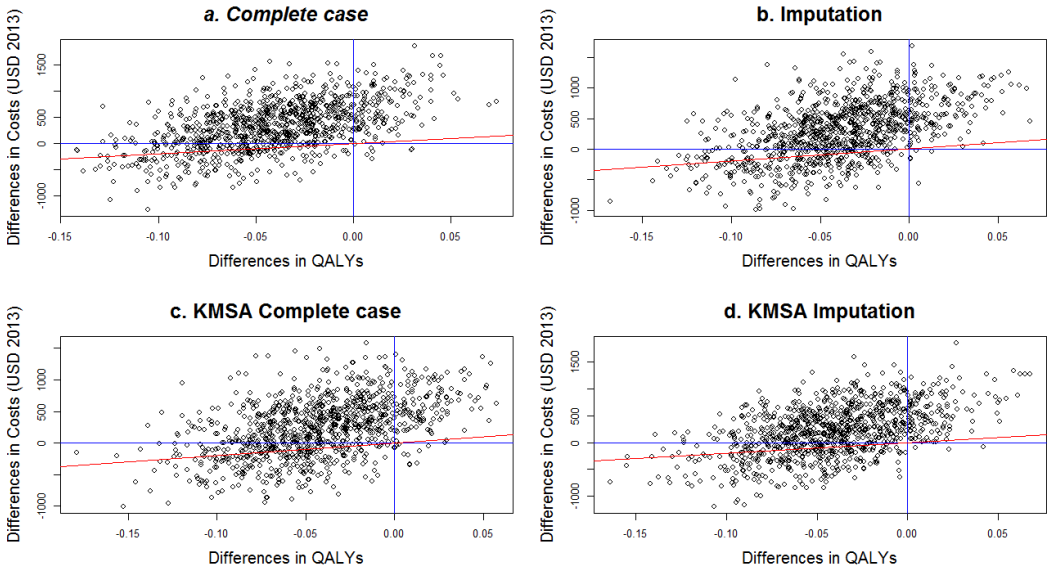


Figure 3-12: Cost-effectiveness plane: 1000 bootstrapped ICER replicates for Thailand tariff in complete cases, multiple imputation analysis, KMSA complete-cases, and KMSA imputation. The graph represents 1,000 bootstrapped simulations of the incremental cost-effectiveness ratio (ICER) (dots) with respect to its components: differences in QALYs on x-axis and incremental costs per patient on y-axis. The diagonal line represents the decision marker's willingness to pay of US$2000 per QALY gained. Points below the diagonal line represent simulations in which the immediate ART strategy was a cost –effective strategy at a threshold of US$2000 per QALY gained.

3.3.6.3 Calculating acceptability curve by non-parametric bootstrap method for complete cases and multiple imputation analysis

In this part, the cost-effectiveness acceptability curve (CEAC) was explored to find out the probability that the immediate ART strategy was cost-effective conditional on the decision maker's maximum willingness to pay. Figure 3-13 demonstrates that immediate ART strategy is unlikely to be a good investment compared to deferred ART strategy in both CC and MI analysis. For 4 different scenarios, the highest probability of immediate ART being cost-effective was when the decision

makers had zero willingness to pay for health gain: that is, were only concerned with costs (38% in KMSA imputation, 31% in imputation, 35% in KMSA complete cases and 30% in complete cases). Furthermore the CEACs did not cut the two horizontal lines at the 0.025 and 0.975 points on the vertical axis, implying that the 95% confidence limits on the ICER did not exist. In general, the results of the CEAC analysis confirm the findings from the incremental cost effectiveness ratios that immediate ART was not a cost-effective strategy for any maximum amount that the decision makers would be willing to pay for an additional benefit.

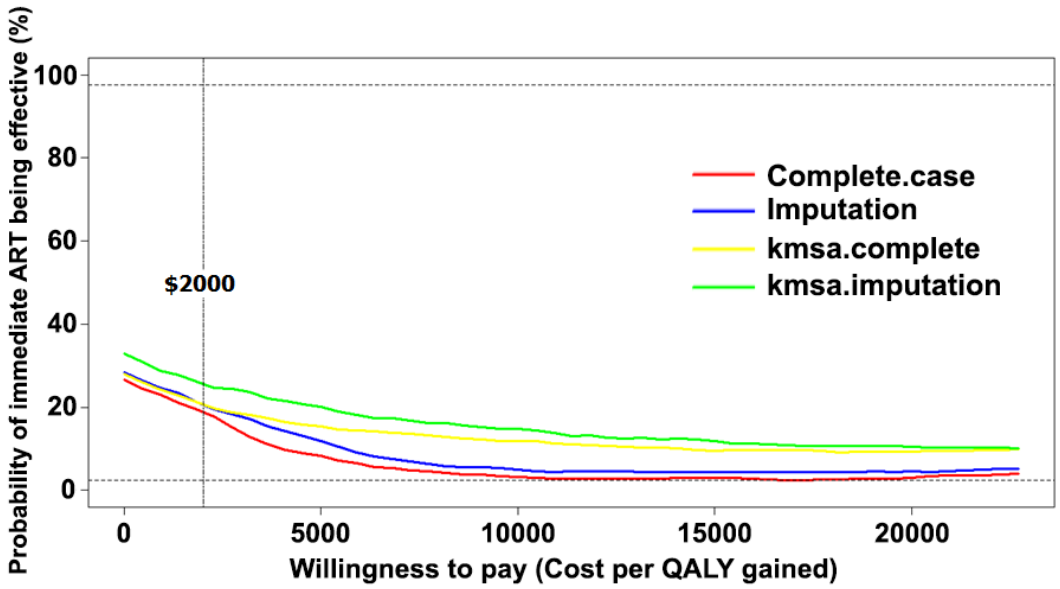


Figure 3-13: Acceptability curve for complete-cases, KMSA complete-cases, imputation and KMSA imputation. The CEACs were derived from the 1000 bootstrapped ICER replications. The x-axis represents different decision maker's maximum WTPs ranging from 0 to $20,000 per QALY gained. The y-axis refers to the probability of the immediate ART being cost-effective. The colours of the lines indicate the type of analysis. (red = complete -cases, blue =imputation, green= KMSA complete- cases, yellow = KMSA imputation). The two horizontal dashed lines indicate the 95% confidence limits for the ICER at the 2.5th or 97.5th percentile.

3.3.6.4 Calculating net monetary benefit for complete cases and multiple imputation: parametric and non-parametric bootstrap approach

The alternative method to estimate confidence intervals for the ICER is by the use of net monetary benefit (NMB). Figure 3-14 demonstrates that the parametric and non-parametric methods yield the same results. The estimates of NMB were negative for any values of WTP ranging from zero to $20,000 per QALY gained. The negative values of NMB implied that the decision maker's willingness to pay for health gain were lower than the cost of immediate ART strategy. This confirms the acceptability curve findings that the immediate ART strategy is not a cost-effective strategy in both CC and MI analysis even after adjusting costs with the censored cases.

Figure 3-15 presents the estimates of net monetary benefits for complete-cases, imputation, adjusted KMSA NMB for complete cases, and adjusted KMSA NMB for imputation based on the non-parametric approach. The NMBs for the adjusted KMSA censored costs for both complete-cases and imputation were negative (-$556 for CC analysis and, -$235 for imputation analysis). After adjusting for survival probability, the immediate ART strategy still costs more than the healthcare decision maker's WTP, indicating that immediate ART strategy was not a cost-effective strategy, but the difference in costs was not as wide as in the unadjusted censored scenarios.

Figure 3-16 illustrates the trend of NMBs and 95% confidence intervals for 4 different scenarios (complete-cases, imputation, KMSA complete-cases, and KMSA imputation). In the CC analysis, both NMB confidence limits were below the x-axis when the WTPs were greater than $5,454/QALY gained. This implied the net benefits were significantly different from zero and we can be 95% confident that immediate ART was not a cost-effective strategy when the WTP was above $5,454/QALY gained. On the other hand, in the imputation analysis, we could be

95% confident that the immediate ART was not a cost-effective strategy when the WTPs were beyond $5,909/QALY gained. However, after adjusting the censored costs, the results of net monetary benefits were not statistically significant in both CC and imputation analysis at the level of 95% confidence. This is because the upper and lower NMB curves did not cross the horizontal axis, indicating the 95% confidence intervals for the ICER were undefined.

In general, the cost effectiveness ratios, the acceptability curve and the net monetary benefit graph provided similar conclusions. Due to the high cost of antiretroviral drugs, immediate ART strategy should not be recommended as a cost-effective strategy to treat HIV in the context of TBM co-infection.

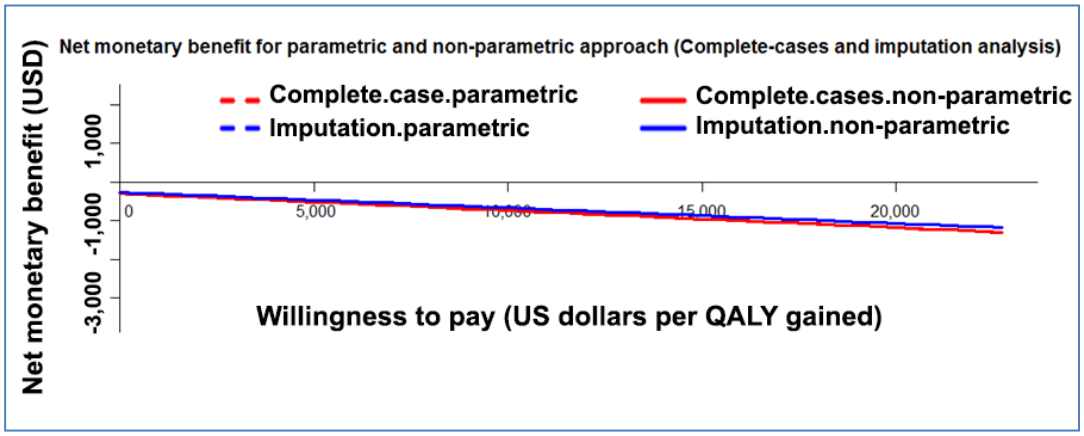


Figure 3-14**:** Net monetary benefit for complete cases and imputation (parametric and non-parametric approach). In this figure, the two lines represent the estimates of net monetary benefit for different values of WTPs. The colours of the lines indicate the type of analysis. (Red = complete -cases, blue =imputation). The type of the line refers to the methodology (the dashed line = parametric, the solid line = nonparametric). The y-axis and the x-axis present the net monetary benefits for different ranges of WTPs ranging from 0 to $20,000 per QALY gained for CC and MI analysis.

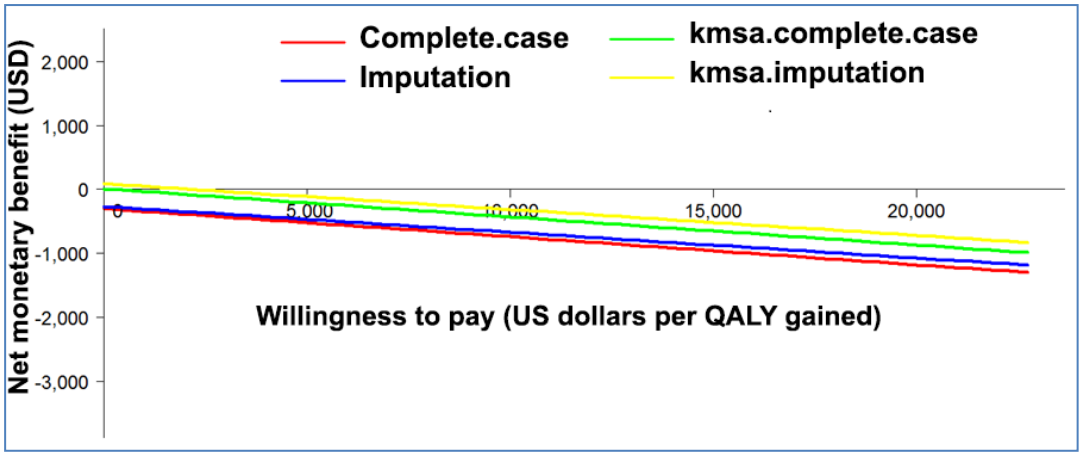


Figure 3-15: Unadjusted NMB and adjusted censored Kaplan Meier NMB for complete cases and imputation (non-parametric approach)**.** In this figure, the lines represent the estimates of net monetary benefit for different values of WTPs. The colours of the lines are the same as in the acceptability curve (red=complete-cases, blue=imputation, green=KMSA complete-cases, yellow=KMSA imputation). The y-axis and the x-axis present the net monetary benefits for different ranges of WTPs ranging from 0 to $20,000 per QALY gained for CC and MI analysis.

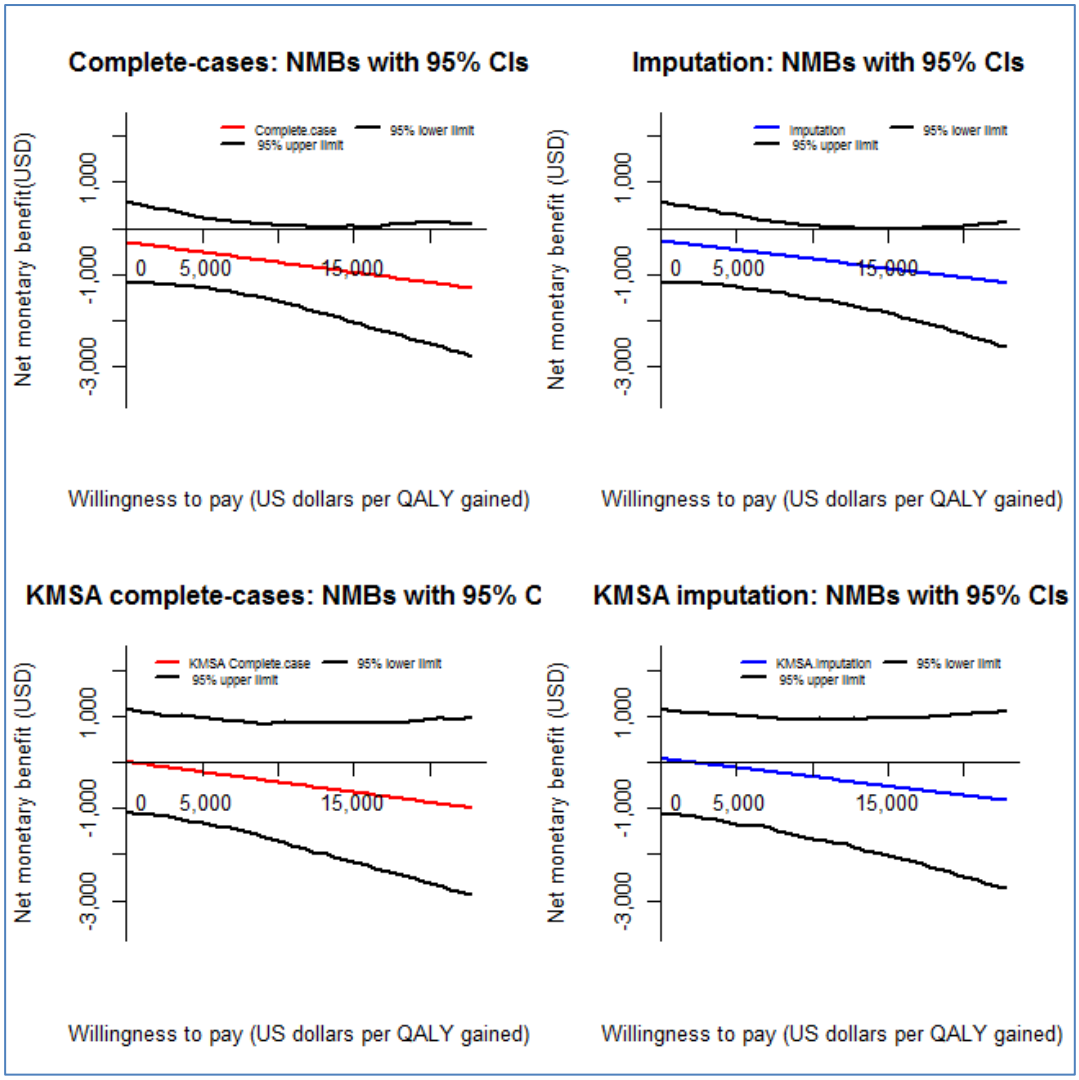


Figure 3-16: Net monetary benefit with 95% confidence intervals for complete cases and imputation and KMSA complete-cases and KMSA imputation. The central line indicates the estimates of net monetary benefit, and the two black lines represent the upper and lower 95% confidence intervals around the average NMB estimators.

3.3.7 **Sub-group analysis**

3.3.7.1 The total costs for sub-groups and difference in total costs for subgroups:

In this part, I examined the differences in total costs for 10 sub- groups with the focus on the KMSA imputation analysis at the adjusted Boferroni 99% confidence intervals (Appendix 10 and Figure 3-17). I focused on the KMSA analysis because

this approach provided more accurate estimates of the mean societal costs because it adjusted the mean costs with the probability of survival in a given time period.

The immediate ART strategy was significantly more expensive for the patients who survived until 9 months. There was no evidence of any impact of treatment strategy in other pre-specified subgroups. The immediate ART strategy was more expensive for patients regardless of their CD4 counts, survival times, and for patients who are living in Ho Chi Minh City with TBM grade 1 or 2 disease. No difference in mortality was found between patients in these sub-groups (a log-rank test KMSA survival was tested). Although the immediate ART group had lower costs than the deferred ART group for patients with TBM grade 3 and living in provinces, this group had a higher mortality. The cheaper costs in the immediate ART strategy were driven by a shorter treatment period, which lowered the cost of the immediate ART strategy. The next part of my analysis will examine the cost-effectiveness of immediate ART strategy for patients in these sub-groups in relation to the decision maker's willingness to pay values at $2,000 per QALY gained.

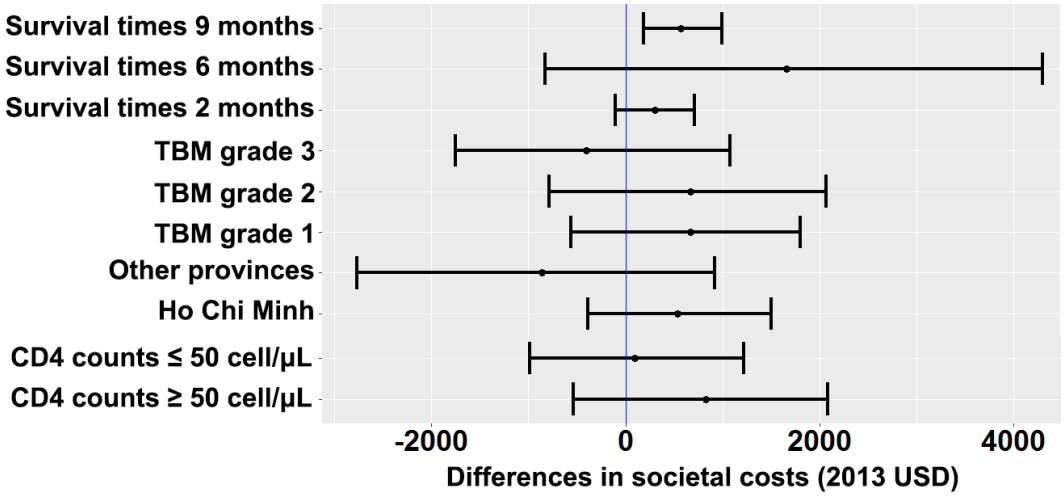


Figure 3-17: Mean difference and 99% confidence intervals of societal costs by subgroups in the KMSA imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND**)** .The dots show the estimates of mean differences in societal costs of the immediate ART group versus the deferred ART group from 1000

bootstrapped replicates. The error bars represent the 99% confidence intervals of the mean. The blue line represents that the mean difference of societal costs were negligible. The dots lie on the left-hand side of the line indicate immediate ART group was cheaper than the deferred ART and vice versa

3.3.7.2 Differences in the health outcomes for sub-groups:

In this part, we examine the differences in QALYs for 10 sub-groups at the adjusted Boferroni 99% confidence intervals. The QALYs were similar across the subgroups. The differences in QALYs were not significant at the 99% CI based on the bootstrapping approach (Figure 3.18, Appendix 11)

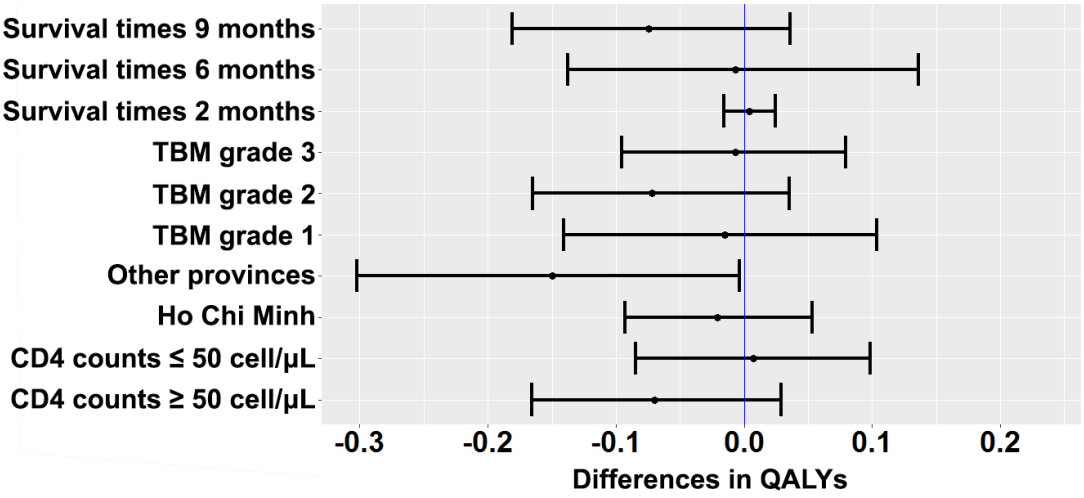


Figure 3-18: Mean differences and 99% confidence intervals of QALYs by sub-groups in KMSA imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND**).** The dots show estimates of mean differences in QALYs of the immediate ART group versus the deferred ART group from 1000 bootstrapped replicates. The error bars represent the 99% confidence intervals of the mean. The blue line represents the mean difference of patient's quality of life was negligible. The dots lie on the left-hand side of the lines indicate that patients in the immediate ART group had lower quality of life than the patients in the deferred ART and vice versa.

3.3.7.3 Cost-effectiveness analysis for sub-groups

Figure 3-19 presents the multiple acceptability curves for 10 different groups for KMSA imputation analysis. These curves represented the probability of immediate ART strategy being cost-effective for different decision maker's WTPs ranging from 0 to $20,000 per QALY gained. The probability of immediate ART strategy

being cost-effective remained lower than 50% in 8 out of 10 sub-groups at WTP values of $2000 per QALY gained. However in scenarios where the patients were from provinces, the acceptability curves were relatively high at 84% at the WTP threshold of $2000 per QALY gained but went down to 50% when WTP values increased. At WTP of $4000 per QALY gained or above, 10/10 scenarios indicated that the immediate ART strategy were comparable or even lower cost-effectiveness than the deferred ART strategy. Overall, the conclusion that the immediate ART strategy was not a cost-effective strategy stands across all sub-group analyses.

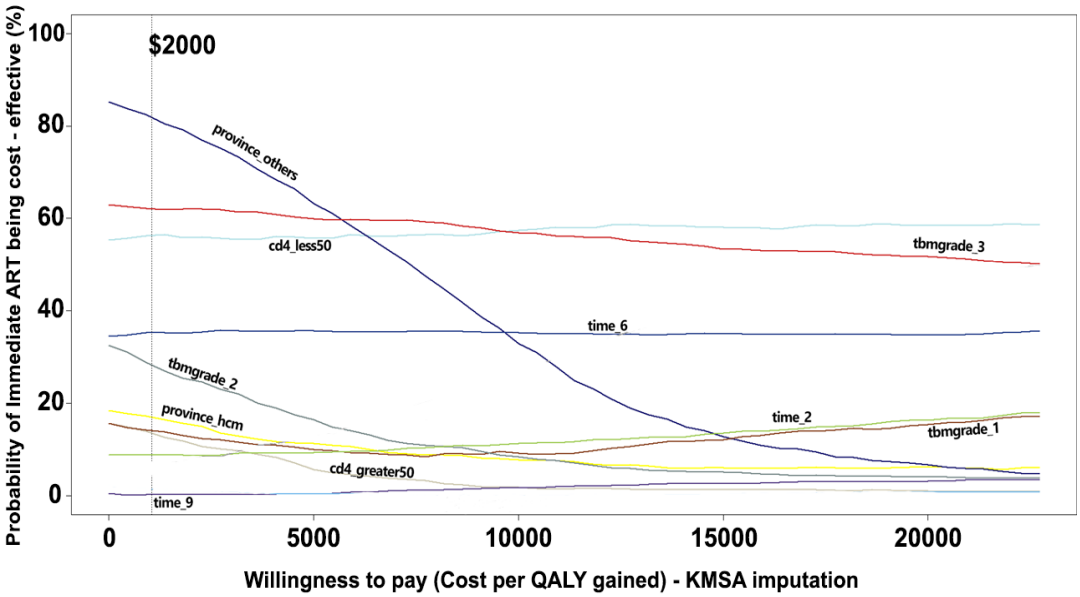


Figure 3-19: Acceptability curves for 12 sub-groups for the KMSA imputation. The CEAC curves were derived from the 1000 bootstrapped ICER replications. The x-axis represents different decision maker's maximum WTPs ranging from 0 to $20,000 per QALY gained. The y-axis refers to the probability that immediate ART was cost-effective. The colours of the lines indicate the 12 sub-groups. The vertical dashed lines represent the willingness to pay thresholds for Vietnam of $2000

3.3.8 **Scenario analysis**

3.3.8.1 The average total costs for each scenario and the cost structure:

Figure 3-20 shows five different scenarios that correspond to changes in the cost of ARV drugs, the one-week costs of doctor visits and the assistance costs. The combination of scenarios did not alter the conclusion that the immediate ART strategy was a more expensive strategy. The differences in all the costs were not significant at the 95% CI based on the bootstrapping method irrespective of scenarios. In scenario 1, when the costs of ARV drugs were reduced 6 times, the societal costs of treating HIV/AIDS and TBM per patient were reduced by half to $1,986 for immediate ART strategy and $2,159 for deferred ART strategy. The deferred ART strategy was slightly more expensive but not statistically significant. The hospital healthcare costs were not the main determinant of the overall costs as these costs account for 30% of the overall costs in scenarios 1 where the costs of the AR drugs were reduced 6 times to its 2013 market prices as in Duong's study [81].

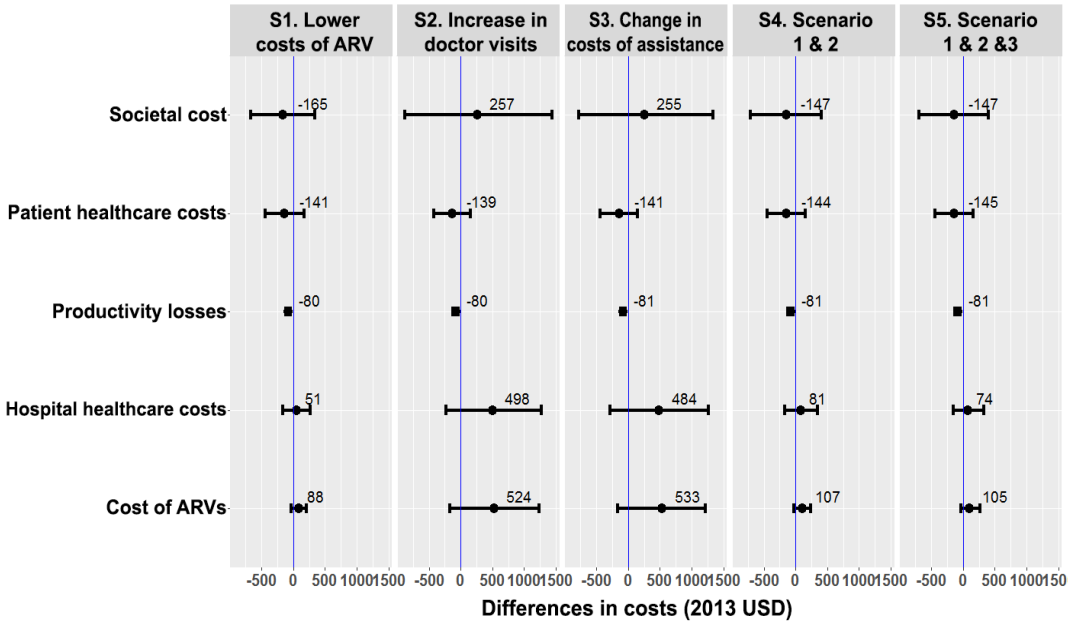


Figure 3-20: Mean difference and 95% confidence intervals of societal costs for 5 different scenarios for KMSA imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND). The y-axis represent the cost types which are societal cost, patient healthcare costs, hospital healthcare costs, income lost, and the cost of ARVs. The x-axis represents the costs. The dots show estimates of the

mean differences in costs of the immediate ART group versus the deferred ART group from 1000 bootstrapped replicates. The error bars represent the 95% confidence intervals of the mean. The blue line represents the mean difference of hospital healthcare when they were negligible. The dots lying on the left-hand side of the line indicate immediate ART was cheaper than deferred ART and vice versa.

3.3.8.2 Cost-effectiveness analysis for 5 different scenarios:

Figure 3-21 presents the multiple acceptability curves for 5 different scenarios for complete-cases and imputation analysis. The five curves represented the probability of immediate ART strategy being cost-effective for different decision maker's WTPs. The probability of immediate ART strategy being cost-effective increased in the scenario 1, 4, and 5 where the costs of the ARV drug were reduced 6 times to its current market price in 2013[81]. The probability of immediate ART remained approximately at 70% for the WTP values of less than $2000 per QALY gained. This indicated that the cost-effectiveness of the immediate ART could be improved when the cost of ARV was reduced to$125 per month. However, as the decision makers were willing to pay more than $4000 per QALY gained, the probability of immediate ART strategy being cost-effective decreased quickly to 50% irrespective of scenarios.

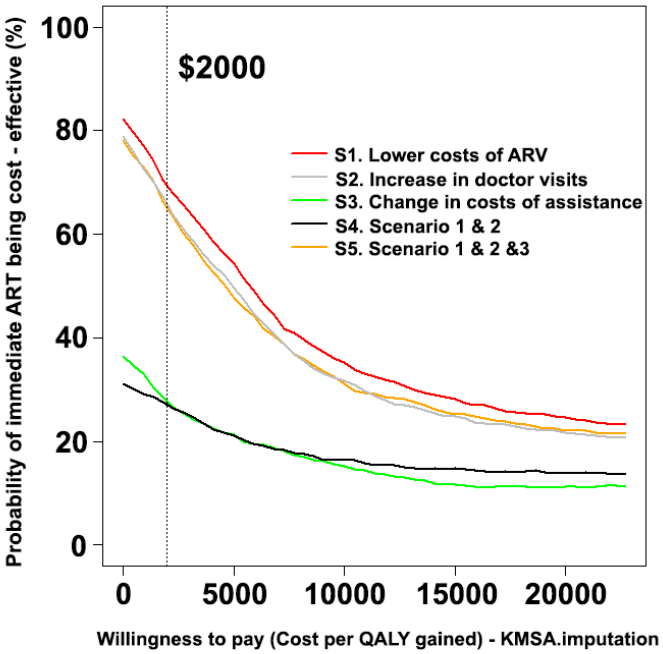


Figure 3-21: Acceptability curves with 95% CI for five scenarios for the KMSA imputation. The CEACs were derived from the 1000 bootstrapped ICER replications. The x-axis represents different decision makers' maximum WTPs ranging from 0 to $20,000 per QALY gained. The y-axis refers to the probability that immediate ART being cost-effective. The colours of the lines indicate the five different scenarios. The vertical dashed lines represent the willingness to pay thresholds in Vietnam of $2,000.

3.3.9 **Trial-based economic analysis for 253 patients and extrapolation**

Introduction: An original randomized controlled trial had a sample size of n=253 patients. The economic data were not available for 49 patients because the economic project was initiated a week after the onset of the clinical trial. A week waiting period meant that 24 patients refused to join the economics project and 25 patients died before the start of the earlier ART versus deferred ART. Therefore, 25 patients who died before entering the economic project were assumed to have zero costs and zero QALYs and their treatment days were averaged at 4 days. The other 24 patients were treated as missing values and utilized the multiple imputation to predict these missing data. The cost-effectiveness analysis and results for 253

patients with the focus on the KMSA and multiple imputation analyses were presented in next part. The procedure of analysis followed similar steps as in the analysis for 204 patients. The steps for adjusting with missing values were investigated as in 3.2.3.1.

Cost-effectiveness results: Table 3-21 showed that the analysis of 253 patients provided the same conclusion as in the analysis for 204 patients regarding the results for hospital healthcare costs, patient healthcare costs, productivity losses and societal costs and QALYs. The immediate ART strategy was more expensive than deferred ART group as treatment strategy for HIV/TBM in terms of societal costs that had been adjusted with the trend of survival probability using the KMSA approach. The cost difference of $557 was not statistically significant (95% CI -502 to 1787). As for the QALYs, this table shows that immediate ART was less effective than deferred ART. At $p<0.05$ there was not a statistically significant differences in QALYs between both groups.

Table 3-21: Societal costs and QALYs: mean differences of costs and QALYs over the duration of the trial (up to 9 months) for by treatment group. The analysis was applicable for 253 participants as in the original random controlled trial.

Costs/ QALYs	**Immediate ART Mean (SD)***	**Deferred ART Mean (SD)***	**Differences in costs or QALYs (Immediate ART – deferred ART) Mean (95%CI)***
Hospital healthcare costs	3,108 (2790)	2619 (2092)	501 (-280 1,303)
Patient healthcare costs	899 (865)	1000 (918)	-106 (-406 172)
Productivity losses	41 (54)	115 (153)	-75 (-113 -40)
Societal costs	4,049 (3571)	3734 (2990)	333 (468)
Societal costs adjusted with	**4,452 (370)**	**3,895 (304)**	**557 (-502 1787)**

KMSA QALYs (using Thai tariff)	**0.16 (0.25)**	**0.2 (0.27)**	**-0.04 (-0.13 0.05)**

*This is the pooled mean and pooled standard deviation from the 20 multiply imputed datasets

Figure 3-22 shows the CEACs that represent the probability that the immediate ART strategy was cost-effective across the decision maker's WTPs. In general the results of the CEAC analysis confirm the findings as in the analysis for 204 patients that the immediate ART was not a cost-effective strategy for any maximum amount that decision makers would be willing to pay for a QALY gained.

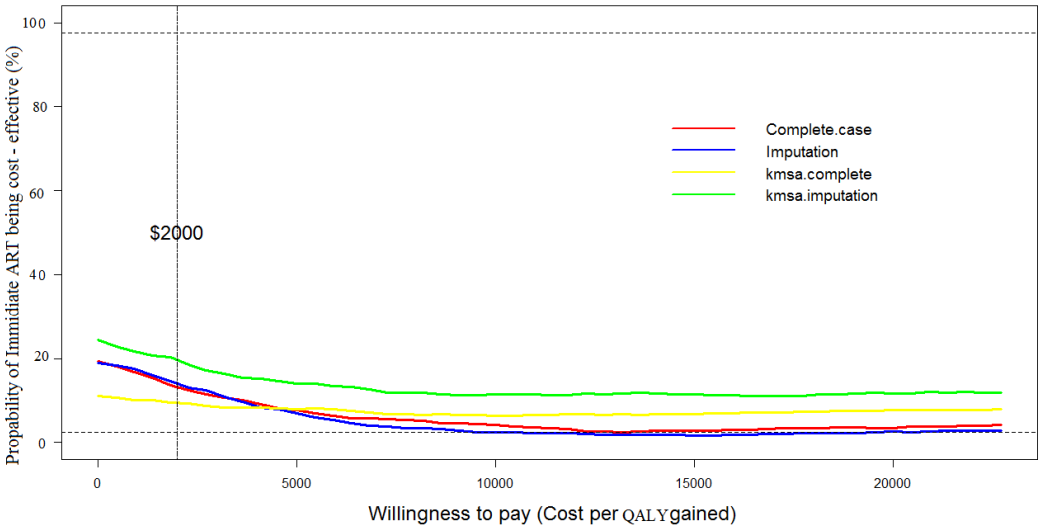


Figure 3-22: Acceptability curve for complete-cases, KMSA complete-cases, imputation and KMSA imputation. The CEACs were derived from the 1000 bootstrapped ICER replications. The x-axis represents different decision maker's maximum WTPs ranging from 0 to $20,000 per QALY gained. The y-axis refers to the probability of the immediate ART being cost-effective. The colours of the lines indicate the type of analysis. (red = complete -cases, blue =imputation, green= KMSA complete- cases, yellow = KMSA imputation). The two horizontal dashed lines indicate the 95% confidence limits for the ICER at the 2.5th or 97.5th percentile.

Extrapolation:

There were 77 patients still alive at the end of 9 months (275 days) (30 patients in immediate ART and 47 patients in deferred ART). This study decided to perform a within trial analysis as regards to both costs and effectiveness because increasingly studies have suggested the immediate ART was not beneficial for patients with HIV-meningitis within trial and is unlikely to be beneficial beyond the study period. A randomized controlled trial in Uganda and South Africa [162] recruited 177 human immunodeficiency virus-infected adults who had cryptococcal meningitis randomly assigned to either earlier ART initiation (1 to 2 weeks after diagnosis) or deferred ART initiation (5 weeks after diagnosis). This trial found that deferring ART for 5 weeks after the diagnosis of cryptococcal meningitis was associated with significantly improved survival at 26 weeks, as compared with initiating ART at 1 to 2 weeks (45% [40 of 88 patients] vs. 30% [27 of 89 patients]; hazard ratio for death, 1.73; 95% confidence interval [CI], 1.06 to 2.82; P=0.03) . Therefore, short delay before imitating ART in HIV-TB meningitis patients should be warranted and its benefit was likely to sustain even beyond the 9 months follow-up.

Nevertheless, a simple extrapolation was executed to examine the cost-effectiveness analysis of the immediate ART strategy that took account of 253 participant's lifetime costs and QALYs. The multiple regression (log-function) was used to model the relationship between the patient's survival days and the patient' probability of being survival at each day during the trial period (until day 275^{th}) conditional on the patient's age, TBM grade, and hospital. This pattern were chosen because it was visually approximated the observed data and had the lowest

AIC score [163]. This type of regression was then used to predict the survival days beyond day 275th for patients in each treatment group until the probability of being survival reached to zero. Here I investigated 2 scenarios: i) Scenario 1: The survival days beyond day 275 for each treatment group was predicted from the log-regression function until the probability of being survival reached to zero.

ii) Scenario 2: The probability of patients in the immediate ART survived beyond day 275th in scenario 1 was assumed to increase 1.3 times because it was found that all-cause mortality risk deferred ART initiation was 1.3 times higher than immediate ART initiation among HIV-TB co-infected patients in this review [164] (Figure 3-23)

Next, the KMSA societal costs and QALYs per day were calculated for each patient per treatment group by taking the total costs and QALY per patient divided by their treatment days. These costs and QALYs per day was assumed to be unchanged in the future as there were no cohorts studies, observational studies available reporting the behavior of the longer-term or lifetime costs and benefit for HIV-TB meningitis patients. The costs and the QALYs per year was discounted at 3%[39].Next, the cost-effectiveness analysis was evaluated as described in the Methodology part.

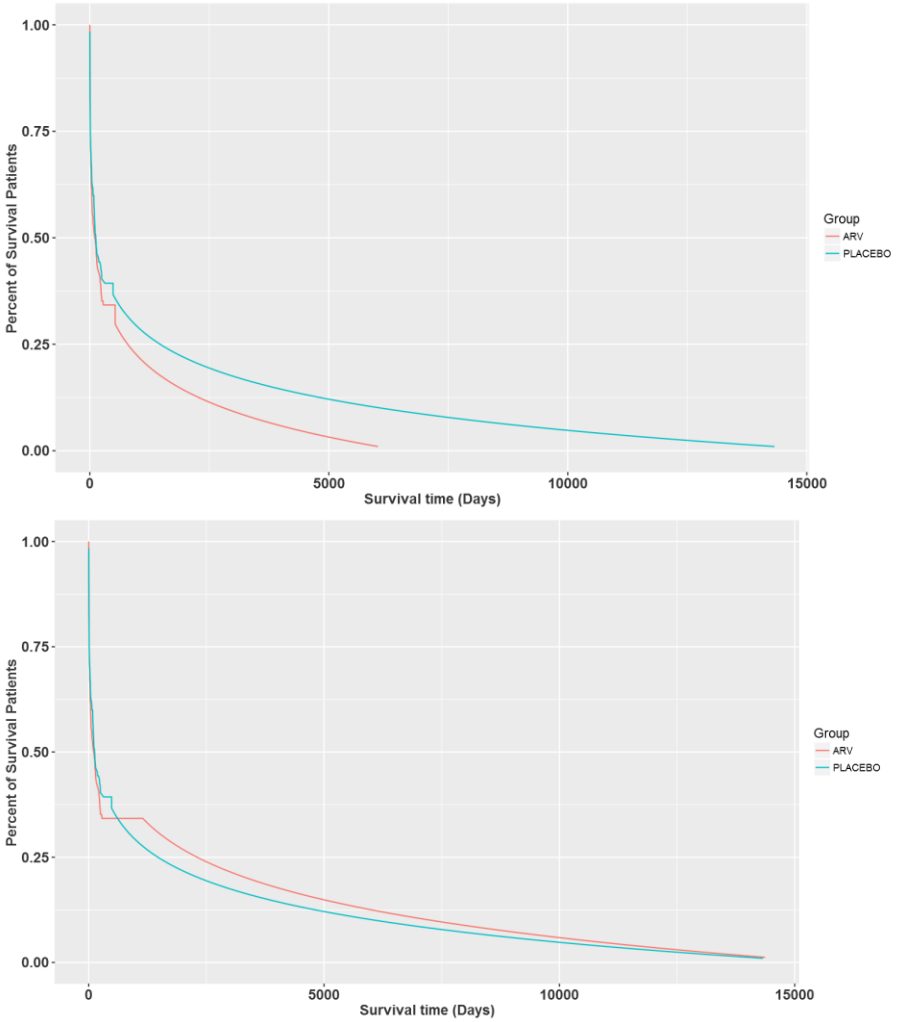


Figure 3-23: Kaplan-Meier survival estimates according to treatment group for 253 patients in the simple multivariable regression (log-function) (first graph) and in the scenario in which the probability of patients surviving in the immediate ART was assumed to increased 1.3 times higher than immediate ART in scenario 1 (second graph). Red solid lines correspond to immediate antiretroviral therapy (ART), green lines to deferred ART treatment. The x-axis represents the survival days the y-axis corresponds to the daily probability of patients being survived.

Cost-effectiveness results:

Table 3-22 showed that for the analysis of lifetime costs and QALYs for 253 patients. The conclusion was still the same for two different scenarios of extrapolation; the immediate ART strategy was more expensive than deferred ART group as treatment strategy for HIV/TBM in terms of societal costs. As for the QALYs, this table shows that immediate ART was less effective than deferred

ART. At $p<0.05$ there was not a statistically significant differences in QALYs between both groups. The CEACs for two different scenarios of extrapolation (Figure 3-24) indicated that immediate ART was not a cost-effective strategy for any maximum amount that decision makers would be willing to pay for an additional benefit as the probability of immediate ART being cost-effective was less than 25%.

Table 3-22: Average lifetime societal costs and QALYs: mean differences of costs and QALYs by treatment group. The analysis was applicable for 253 participants as in the original random controlled trial

Costs/QALYs	Immediate ART Mean	Deferred ART Mean	Differences in costs or QALYs (Immediate ART – deferred ART) Mean (95%CI)
Scenario 1 (Survival days beyond day 275th for each treatment strategy were predicted from log-multiple regression)			
Number of survival days	5,580	13,921	
Extrapolated costs beyond day 275th	47.3	24.97	22.35 (5.47 41.95)
KMSA societal cost (scenario 1)	3791.2	3411.8	379.4 (-496.6 1217.6)
QALYs (scenario 1)	0.147	0.177	-0.03 (-0.09 0.03)
Scenario 2 (Predicted survival probabilities beyond day 275th in the immediate ART in scenario 1 were assumed to increase 1.3 times)			
Number of survival days	13,981	13,921	
Extrapolated costs beyond day 275th	40.19	25.02	15.175 (0.57 30.56)
KMSA societal cost (scenario 2)	3804.2	3438	366.2 (-478 1161.2)
QALYs (scenario 2)	0.1	0.2	-0.03 (-0.1 0.04)

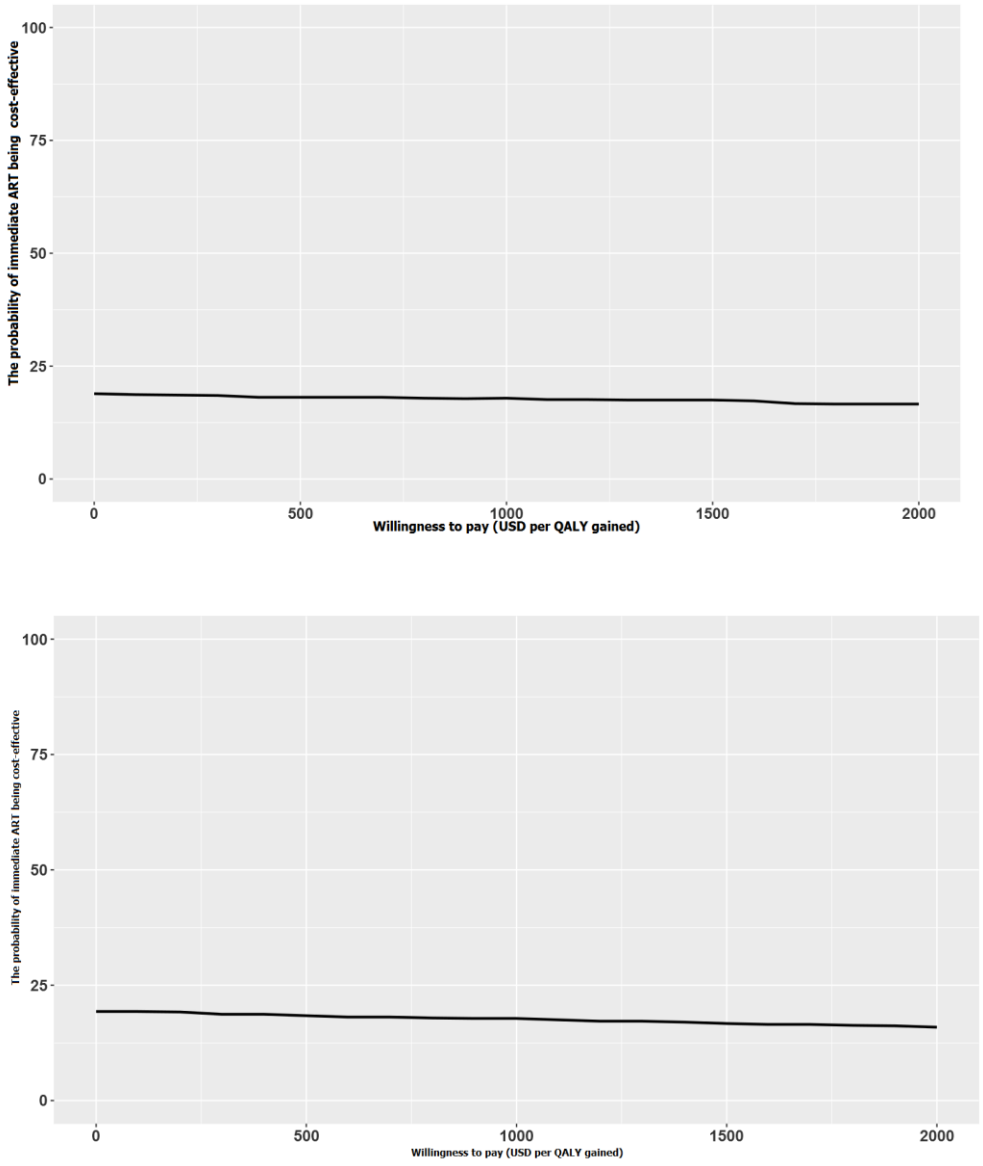


Figure 3-24: Acceptability curve for two different scenarios of extrapolations for 253 patients in the simple multivariable regression (function) (first graph) and in the scenario in which the probability of patients in the deferred ART was assumed to increase by 1.3 times more than the immediate ART (second graph). The x-axis represents the decision maker's willingness to pay (0 to $2000 per QALY gained). The y-axis presents the probability of immediate being cost-effective (%)

3.4 **Discussion**

3.4.1 **Discussion about the cost results**

The goals of this study were to estimate the costs directly associated with the treatment of HIV/TBM during the 9 months of the trial. After adjusting the censored cases, the societal costs were estimated at around $4,223 (CC) and $3,984 (MI) for the immediate ART intervention, and $4,273 (CC) and $4,065 (MI) for the deferred ART intervention over the whole study period of 9 months. The immediate ART intervention generated incremental costs of $239 (95% CI -775 to 1,352 in CC analysis) and $208 (95% CI -819 to 1,277 in MI analysis). The differences in societal costs were not statistically significant according to the bootstrapping methods. This reflects the fact that the immediate ART strategy required higher resource utilization during treatment. The increased costs of immediate ART strategy were attributable to starting ART 2 months earlier and higher frequencies of grade 3 and 4 adverse events during the first 2 months.

One surprising thing to note is that patients and their carers in the immediate ART group incurred significantly less loss of income during the trial and experienced lower costs for waiting for examination or when accompanying patients to trial visits despite the absence of a statistically significant differences in overall costs between the two treatments. This could be explained by the fact that patients in immediate ART group were too sick to make trips for hospital health examination, leading to lower income lost.

This study found that 80% of the total costs were made up of the hospital healthcare costs [$3,108 (CC & MI) for immediate ART and $2,619 (CC) and $2,615 (MI) for deferred ART]. 80% of hospital healthcare costs were the costs of

ARV medication. The high cost of ARV drugs was also seen in findings from Duong (2014) and Nguyen (2014). In this study, ARV drugs are the most expensive element in the total costs, and therefore the wide difference in antiretroviral therapy administration between the two groups drove the wide differences in overall total costs. After reducing the price of ARV drugs to the 2013 market price in the scenario analysis, the societal cost of $2000 per patient was still higher than the annual income per capita in Vietnam in 2013 ($1,907 [4]). This high cost implied that treating HIV/AIDS-co-infected with TBM would cause substantial health expenditures for both the health system and patients.

This total cost result was a little higher than the 3 previous costing studies of HIV care in Vietnam [80,82,109] and 5 global costing studies of TB and HIV care [76,77,88,89,100]. The average total cost associated with management of tuberculosis and HIV co-infected individuals was estimated in the range of $411 to $946 per person for the duration of TB treatment (6 to 8 months) after aggregating results from these 8 previous studies. The fact that our total cost was higher than these studies was likely because our study captures the full costs of the ARV drug costs and the cost of TB treatment (sputum smear microscopy and first-line TB drugs), while they are provided free-of-charge or partly funded in these countries, and therefore these costs might not have been included in their calculations. This is more likely due to the fact that in our study patients have TB meningitis. TB meningitis is much more severe than pulmonary TB. It causes brain damage which results in disability. Also, patients with TBM are probably much more immunosuppressed than the average patients with pulmonary TB. The death rate from TBM is probably at least 10 times higher than the death rate from pulmonary. Our study focused on the disease HIV/TBM that was perceived as more severe than

the HIV/TB. Our study also captured the productivity costs for both patients and their carers. The cost results from our study suggest that the government should continue the current policy, which provides ARV drugs and TB treatments free of charge, to reduce financial burden for both hospitals and patients co-infected with HIV and TBM.

3.4.2 **Discussion about the quality adjusted life years results:**

Our study found EQ5D scores of 0.5 at 2 months, and EQ5D scores of 0.8 at 9 months, implying that patients with HIV/AIDS and TBM on the ART and TB therapy decreased the patient's quality of life by 50% and 20 % from their healthy life at 2months, and 9 months. The results from the visual analog score also confirmed that HIV/TBM patients in both treatment groups felt better from 2 months to 9 months (64.1 at 2 months and 87.64 at 9 months for immediate ART, and 68.2 at 2 months to 88.4 at 9 months for deferred ART in MI analysis). These changes could be valid when compared with CD4 levels and viral loads at 2 months and 9 months. Although ART has the benefit to prolong HIV patients life expectancy, when treating with TB therapy, the combination of these drugs tend to cause various adverse effects (i.e., adverse drug reactions and drug interactions) and partly affect the daily activities, thereby reducing patient quality of life. The two most affected domains were pain and depression.

Overall, immediate ART provides a lower effectiveness of 0.04 QALYs than deferred ART. However, the difference in QALYs was not statistically significant between both groups [-0.041 QALY 95%CI -0.114 to 0.032 Thailand tariff in CC analysis].

3.4.3 **Discussion about the incremental cost-effectiveness ratio results:**

The study found that after adjusting for censored cases, immediate ART provides a lower effectiveness of 0.04 QALY at incremental costs of $239 and $208 in CC and imputation analysis.As a result, the incremental cost-effectiveness of immediate ART was a negative ratio of $5,975 per QALY gained, and $5,200 per QALY gained for KMSA complete-cases and KMSA imputation. This negative incremental cost-effectiveness ratio would also imply that deferred ART costs an additional $5,975 per QALY gained, and an additional $5,200 per QALY gained for KMSA complete-cases and imputation respectively. However, the interpretation of an individual ICER estimate is ambiguous without information regarding whether the immediate ART is cost-effective for society. Moreover, the 95 percent confidence intervals around the ICERs are not very informative as they could not differentiate between the negative ICERs for interventions with more costly and less effective, or more effective and less costly. The 95 percent confidence intervals around the ICERs are not very informative as they could not differentiate between the negative ICERs for interventions with more costly and less effective, or more effective and less costly.

As a result, the acceptability curve and the net monetary benefits framework were employed to summarise the overall evidence of cost-effectiveness, even if the 95%CI around the point estimate of ICER were undefined. Our study found that for any values of willingness to pay ranging from 0 to $22,000, the probability of immediate ART being cost-effective was almost zero in all 4 tested scenarios: complete-cases, imputation, KMSA complete-cases and KMSA imputation. Therefore I concluded that immediate ART was not cost-effective over a range of willingness to pay ranging from 0 USD (if society were only willing to consider interventions that were cost-saving) to $22,000 per QALY gained. The results of

the net monetary benefits also confirmed the findings from the acceptability curve across different sub-groups and scenario analysis. Therefore in this study we concluded that immediate ART was not cost-effective over a range of WTPs from 0 USD to $22,000 per QALY gained.

This result was in conflict with the Sax (2011) study that investigated the timing of ART in HIV patients with acute opportunistic infections (OI) in USA. This study favoured early ART starting at 2 weeks versus the deferred ART starting at 4 weeks after OI diagnosis for HIV patients presenting to care with acute OIs because early ART reduced death and AIDS progression compared to ART initiation 1 month later. However, patients with tuberculosis were excluded from the trial, and therefore the results of this trial may not be applicable to HIV patients with TBM.

3.4.4 **Strengths of the study:**

This is the first study worldwide to investigate the cost-effectiveness of different timing of initiation of ART in patients with HIV/TBM. Furthermore this study generated a more comprehensive picture of the hospital healthcare costs, patient healthcare costs and productivity losses for HIV/AIDS and TBM care in a developing country. This is a relevant issue in Vietnam, as a small proportion of the total cost of ART is sponsored by government funds. International funding is likely to decrease in the near future; therefore it is important to investigate the payment capacity of the HIV/AIDS patients if they had to pay themselves, or to formulate a comprehensive copayment strategy for Vietnam or other developing countries with similar programs.

3.4.5 **Limitations of the study:**

The main limitation of this study lies in the methods of cost adjustment for healthcare costs incurred by the patients and caregivers. These costs were estimated from a one-week sampling period immediately before the 2 month, 6 month and 9 month follow up visits to costs across all patients over the periods of interest, but may also generate an artificial and extremely unlikely distribution of costs at the individual patient level. This was the main limitation of the sampling approach and the cost adjustment. Secondly, the cost estimates in this study could be considered conservative as the costs only included the number of visits specified in the trial protocol, while during the study patients could make extra visits to private clinics/hospitals. Secondly, the missing values in medication costs coupled with the issue of one-week sampling will reduce the accuracy of the estimate of this cost. The third limitation of this study was the unrecorded EQ5D score at baseline. As a result, the lowest EQ5D score was imputed, based on assumptions of disease severity at study enrolment. However the most important thing is the comparison between patients at outcome. This is a randomized controlled trial of a reasonable size and therefore it is likely the health utility scores would have been the same between patient groups. Fourth, the EQ5D has been critiqued as less sensitive than disease-specific measurements resulting in a possible underestimate or overestimation of patients' HRQL. Nonetheless, these utility values derived from clinical trials could be used for economic modeling in the future and the ability to compare across diseases and across countries may outweigh the sensitivity concerns. Our economic evaluation were only able to obtain the aggregated costs from the patient's hospital bills so the physical resources used in an intervention as well as unit price could not show clearly in the analysis. Finally, our sample primarily consisted of those living near the hospital in an urban setting (Ho Chi

Minh City 85%). Therefore our results may not be representative of costs associated with HIV/TBM in rural settings.

The number of participants in this cost-effectiveness analysis was based on the number of patients determined initially by the clinical trial. The trial recruited 253 patients based on two previous randomised controlled trials in Vietnam for HIV-TB patients which found that the case-fatality rate for patients with HIV-associated TBM was 65% [62,66]. Based on these two trials, the authors of the trial aimed to recruit 253 patients as a reasonable sample size.

However, the sample size may be small in other settings and could be the reason for the lack of significance in the differences between the two patient groups. To my knowledge, there was only one study conducted in South Africa that was similar to our study in terms of interventions but have a greater sample size. Naidoo et all (2015) [93] investigated the cost-effectiveness of three strategies which were initiated ART within 4 weeks after the initiation of TB treatment (214 patients), initiation of the ART within 4 weeks of the continuation phase of TB treatment (215 patients), or on completion of TB treatment (213 patients) for patients co-infected with TB and HIV [93]. Therefore, data from larger sample size with appropriate comparison groups, and adequate follow-up would underscore the conclusion that delaying ART until the end of intensive phase of TB treatment for HIV-co-infected TB patients meningitis was the most cost-effectives strategy.

The unit cost and the quantity of resources were not reported separately in this analysis. It is possible that there was some degree of under-or over-estimation, perhaps related to the use of a non-standardized questionnaire or gaps in the record-keeping at the hospital during the period 2005 to 2007 in Vietnam. However, it is worth noting that previous evaluations of cost-effectiveness in Vietnam rarely included both the unit cost and the quantity of resources [2]. This may reflect a lack of proper understanding from the health economic researchers of how the healthcare costs could be appropriately quantified [1] and could be used to estimate the standardized hospital unit cost/prices in Vietnam.

Second, the productivity losses were not fully quantified in terms of both paid and unpaid work. Our analysis did not consider the productivity losses for unpaid work such as household work, care work, or volunteer work while aiming to take a societal perspective [113]. In practice this type of productivity loss was often excluded as there is little guidance regarding the inclusion of unpaid labour in economic evaluations[113]. However given the strong effects of certain diseases like HIV-TB meningitis on patient's quality of life, these patients could hardly pursue any paid work therefore treatments definitely affect their the ability to perform unpaid work. Ignoring the unpaid work may violate the value of economic evaluations and the ability to present a well-informed societal decision making.

Conclusion of Chapter 3

The study found that immediate ART is unlikely to be an appropriate or cost-effective treatment for patients infected with HIV and TBM as this strategy generates more cost and is less effectiveness than deferred ART. However, deferring ART until two months following the diagnosis of TBM (and instigation of treatment) might incur higher costs in income lost and costs of examinations and

accompanying patients to health visits than implementing ART immediately. The high societal costs in our results implied that ART and TBM treatments are likely to impose a significant financial burden on patients. Therefore, support from government or other funding sources should be sustainably maintained.

Chapter 4: **Background and literature review for cost effectiveness of national malaria programs**

Switching from single to multiple first line therapies (MFT) for antimalarial treatment has been proposed as a strategy to delay the development of antimalarial resistance, but whether this is likely to be cost-effective has not been explored. Changing antimalarial drug policy can incur high costs, and these costs accumulate each time policy needs to be changed due to developing resistance. The distribution of multiple drugs in the supply chain that would be necessary for MFT could also have cost implications. Furthermore, while previous modelling work from our group demonstrated that MFT can result in lower malaria incidence and deaths, this impact has not been summarized in standard measures such as DALYs or QALYs that are informative for economic evaluation.

This chapter aims 1) to cover briefly the background of malaria, malaria treatment guidelines and historical drug resistance; 2) to describe the multiple first-line therapies strategy 3) to review the literature on the economic evaluations of switching first line therapy due to antimalarial resistance; 4) to review the literature on the cost of introducing new national health policies for treating malaria; 5) to review the literature on the costs of producing and delivering ACTs.

Cost estimates and other relevant data extracted from these reviews will then feed into an economic evaluation of MFT in Chapter 5.

4.1 **Background of malaria**

4.1.1 **Overview of malaria cycle and the clinical characteristics of malaria**

Malaria is caused by the organisms of the genus Plasmodium, transmitted by the female Anopheles mosquito-borne disease that transmits parasites (or the sporozoite form of the parasites) into the human [165]. The five common species of Plasmodium genus that cause malaria in humans are *Plasmodium falciparum* which causes the severest type of malaria, *Plasmodium vivax, Plasmodium malariae, Plasmodium oval and Plasmodium knowles*i which cause less severe symptoms[166]. In humans, sporozoites are transported in the bloodstream to the patient's liver where they grow, multiply and attack first in the liver cells. In this stage, the sporozoites mature into schizonts, and later invade red blood cells as merozoites. The malaria parasites multiply 10-fold every 2 days, destroying red blood cells and infecting new cells throughout the body. In the blood-stage, the parasites differentiate into sexual parasites (gametocytes) where a single infection can produce both male and female gametocytes in the infected human blood and is transmitted to the mosquito through their blood meals. After 10 to 18 days, the parasites (sporozoites) are present in the mosquito's salivary glands; they are mature and ready to be passed on to someone else. Malaria symptoms appear anywhere from about a week to several months after infection, but usually in 7-21 day. People with malaria often experience fever, chills, and flu-like illness, considered as uncomplicated malaria. Without prompt access to malaria treatment and adhere to treatment appropriately, they may develop severe complications and die. Severe complications include cerebral malaria [167].

WHO estimated 3.2 billion people at risk of infection globally[168]. In 2014 there were 214 million new cases and an estimated 438,000 malaria deaths worldwide. The African Region accounted for most cases (88%), followed by the South-East Asia Region (10%) and the Eastern Mediterranean Region (2%).

4.1.2 **Malaria treatment guidelines and drug resistance**

One of the earliest antimalarial drug was the synthetic drug chloroquine (CQ) which was discovered in the 1930s. The first resistant strains to CQ were detected around the Cambodia-Thailand border in the 1950s and spread throughout Southeast. Then, Sulfadoxine/pyrimethamine (SP) replaced CQ as the first-line treatment for malaria in some African countries during the 1980s. Parasites resistant to SP emerged a few years after introduction[166]. Artemisinin was discovered by pharmacologist TuYouyouand later combined with another (non-artemisinin) drug into a single tablet which was registered as a medicine in China in 1992 under the name "Coartem". This and other artemisinin combination treatments (ACT) are now widely used to treat uncomplicated *falciparum* malaria instead of monotherapy to increase the drug efficacy and delay the emergence of drug resistant parasite.

Drug resistance is defined as the ability of a parasite strain to survive and/or multiply despite taking the recommended treatment doses[168]. Drug resistance can first emerge (*de novo* emergence) when a genetic change occurs in a single parasite in a single patient. If this event happens, this single malaria parasite can generate multiple descendants. Mosquitoes can then acquire resistant parasites from a single individual and transmit them to other people. The robust, resistant clone can spread similarly to any malaria strain, but in environments where drug pressure

is high and if the fitness cost is low it will benefit from a survival advantage. It is then a matter of time until the genetically resistant strains will spread. To date, parasite resistance to artemisinin has been detected in 5 countries of the Greater Mekong sub-region[169]. Whole genome sequencing of the artemisinin-resistant parasite revealed mutations in the Kelch 13 (K13) propeller protein associated with the artemisinin resistance in both clinical and field isolates. The Kelch family protein was responsible for organizing and interacting with other proteins. Nonsynonymous polymorphism at Y439H, R539T, I543T and C580Y position in the K13 propeller domain have associated with higher risk of resistance to artemisinin.

4.1.3 **Overview of multiple first-line therapies**

Current and historical practice in Africa has recommended a single first-line therapy or drug for uncomplicated malaria and when drug-resistance levels rise, to replace the officially recommended drug with a new one to which resistance has not yet emerged.

Boni and colleagues [170] recommended the use of multiple first-line therapies (MFT) to slow the evolution of resistance. MFT was defined as a drug policy in which several therapies were made available in equal proportions in the population and in both the public and the private sectors. Boni and colleagues [170] constructed an evolutionary-epidemiological modeling framework for malaria and compared the benefits of MFT over cycling therapies in terms of biological and clinical aspects in the context of resistance evolution over 20 years. The cycling strategies were defined as switching on a predetermined schedule or when treatment failures increases. This study demonstrated that the MFT strategy minimized treatment failures and overall clinical disease for 92.6% of parameter

combinations of basic reproductive number (Ro) (1.1 to 100), *denovo* mutation rate to specific drugs (10^{-6} to 10^{-1}), treatment coverage (0.2 to 1) and the cost of resistance to specific drugs (0.05 to 0.2) and the parasite population's inbreeding coefficient (0 to 1). MFT strategy made the evolution of resistance more difficult for the parasites because the strategy promoted a diversity of drugs in the parasite's environment, making it hard for parasites to adapt to any one part of the environment, as there was a smaller chance of the parasites encountering a different drug to the one in the previous host on every new infection. As a result, the advantage of deploying MFT were i) to delay the emergence of resistance strains, ii) to slow down the spread of resistance iii) to reduce the overall clinical burden, and failed treatments.

Nguyen and colleagues [63] advanced from the analysis by Boni and colleagues and developed an individual-based micro-simulation of regional malaria transmission, evolution and clinical management. This study compared three population-level treatment strategies: MFT strategy against cycling or sequential use of single first-line ACTs. The cycling strategy involved the national drugs being changed every 5 years. The sequential strategy was when the treatment failures reach 10% as recommended by WHO (2014). The results of this study showed that using the MFT strategy, the median blood-slide malaria prevalence across 100 simulations over 20 years was consistently the lowest, at less than 5% level of blood slide positivity (in a low-to-moderate transmission setting). Secondly, for treatment coverage between 50% and 70%, MFT strategies yielded a median number of treatment failures between 16% and 41% lower than either cycling strategy or sequential strategy. With higher cost of resistance, MFT

strategy was even more superior. This finding suggested that MFT prolongs the efficacy of ACT drugs.

4.2 Economic evaluations of implementing national level malaria drug policies to tackle resistance: a systematic review of empiric studies

4.2.1 Introduction

Cost-effectiveness analyses for new antimalarials have mostly accounted for the higher unit costs of the drugs and benefits for the individual patient [171–177]. However, the process of implementation is itself not without costs. Economic evaluations of strategies for implementing new national antimalarial drug policies, focusing on the costs of policy change and the long -term benefits that account for the possible spread of resistance at a societal level are scarce. The following literature reviews will provide the evidence base for the cost and cost-effectiveness assumptions in Chapter 5.

Aims: The aim is to evaluate the costs and cost-effectiveness of introducing antimalarial drug policies at the national level, focusing on the process of implementation.

Outline: Based on these aims, I conducted a systematic review of empiric studies broken down into 3 major topic headings: i) The first part presents a review of economic evaluation of switching drug regimen due to antimalarial resistance ii) The second part present a review of the costs of changing first-line drug policy in malaria. ii) The third review focuses specifically on the purchase and delivery costs of ACTs. These two reviews required different search strategies, as detailed below.

4.2.2 **Economic evaluations of switching drug regimen due to antimalarial resistance**

The objective of this section was to conduct a systematic review of the economic evaluations of switching drug policies due to antimalarial resistance. This review specifically focused on studies that employed a mathematical model that simulated disease transmission and the development of drug resistance to assess the tradeoff between risk of resistance and operational costs of switching to another drug policy. This review aims to assess the model structure and process and to quantify the contributions of key model parameters to the outputs [178].

Search strategy and inclusion criteria: Following the CHEERS guidelines [53]I searched PubMed for articles addressing the economic evaluation of antimalarial resistance of malaria in developing countries published between 2000 and 2014 The search strategy contain terms for both the subject topic area as well as relevant economic terms. Search terms used were, 'malaria', 'economic evaluation of resistance', 'costs', 'developing countries', "LMICs', 'Vietnam'.

Inclusion criteria for considering studies for this systematic review: Peer-review articles, systematic review, and international reports (WHO) assessed the economic evaluation of antimalarial resistance of malaria. Studies where resource use was derived from other studies, modeling or expert opinion were included. Prices or unit costs could be derived from any sources, including administrative data, national account data or published studies.

Data extraction and analysis: Data extraction sheet was used, the composition of which was informed by the data-extraction guidelines for economic evaluations in the Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care Systematic Reviews of Interventions [75]. Titles and abstracts of all

identified articles were checked. The full texts of all potential eligible studies and for those studies where relevance were obtained. The following information was extracted from each of the identified studies: author(s), year of publication, study question, patient population and sample size, intervention, comparator and setting (country where study was based, urban/rural area), modeling studies used to derive resource use; sources and quality of clinical data,, cost included, time horizon, use of discounting and year of costing, The data were extracted into summary tables according to the pre-defined criteria.

4.2.2.1 Results

Mathematical modelling of malaria transmission and economic modelling:

The results of the database search identified 149 potentially relevant articles according to their title and abstract. The full texts of 4 articles [177,179–181] deemed relevant as they were model-based economic evaluations that assessed the development of drug resistance and the drug policy switching. The 145 papers were excluded because many of these studies have reported data on the economic burden of malaria and the cost of malaria programmes without considering resistance; studies were not model-based economic evaluations and did not present final costs and benefits.

Of 4 papers reviewed, two used the decision trees [182,183]. These models were unable to capture the transmission effects while the remaining two malaria studies used dynamic compartmental models [179,184]. Two studies referred to previously published work for a full description of the transmission model (Table 4-1). No studies assessed economic evaluations using the individual-based model.

Table 4-1: Economic evaluations of switching drug regimen due to antimalarial resistance using mathematical modeling

Study	New drug policy and aims	Modelling type	Resistance considered	Previous modeling work	Model structure	Duration	Economic parameters	Epidemiological parameters	Conclusion & limitations
Spilotopoulou et al (2013) [179]	Multiple drugs	Compartmental dynamic transmission of malaria and resistance spread	Yes	Boni et al (2013)	A disease transmission model that includes compartments for susceptible, infected with resistant strain or drug susceptible strain,	5 years 10 years 15 years	Procurement costs ($1 to $10 to$100) Stock holding costs Volume discount (0.1% or 1% or 10% for 100,000 units bought)	Constant transmission rate Probability that denovo resistance emerges when drug i is used. Rate at which treated individuals return to susceptible state. Death rate, Population infected with a susceptible strain. Population infected with a strain that is resistant to drug i. Fraction of patient who are treated with drug i	Under a wide variety of scenarios for disease prevalence and drug cost, it is optimal to simultaneously deploy multiple drugs in the population.
Mori et al (2014) [185]	DHA-PPQ vs AL	Markov model	No		Four mutually exclusive health states: “well malaria, “ severe malaria and “death	1 year	Costs were collected for the treatment of uncomplicated and severe malaria, Capital costs ,Drug costs, Disability weight 0.005 and 0.21.	Case fatality rates, and other probabilities from untreated/treated severe malaria to death. Early treatment failure to severe	
Coleman et al (2004) [183]	SP vs AL	Decision tree model.	Yes . Temporal dynamics of drug	Goodman et al (2001) [182]	Dynamics of drug resistance were depicted as a general logistic	5 years 10 years and 15 years	The initial frequency of ACT drug resistance is set at 0.01 The initial level of SP	The probability of treatment failure, *F*, with a given first line	ACTs achieved 95% likely to be cost-effective under most conditions,

Study	New drug policy and aims	Modelling type	Resistance considered	Previous modeling work	Model structure	Duration	Economic parameters	Epidemiological parameters	Conclusion & limitations
			resistance was considered which the starting frequency of resistance and maximum growth may be altered		growth function, The growth rate of resistance to ACT relative to that of current therapies varied		resistance and the ratio of the growth rate of artemisinin-based combination therapy (ACT) resistance relative to the growth rate of SP (*rACT/rSP*).	drug, *i*, at time *t* . The proportion of malaria parasites, *R*, resistant to drug *i* at time *t*; the probability, *m*, that a patient complies at the recommended dose with drug therapy *i*;	other than very low levels of initial resistance to SP and a five-year time frame.
Yeung et al (2009)		Compartmental dynamic transmission of malaria and resistance spread	Yes		Resistance occurs and develops in two stages de novo emergence and spread, Incorporation of immunity function Inclusion of parasite density malaria morbidity and severe malaria	10 years	Cost of drugs using ACTs, plus the cost of the initial treatment to public providers (consultation, diagnosis and inpatient costs for small patients), plus the cost of treatment failures covering second-line drugs, cost of inpatient care and complications under different treatment strategies	1)The initial estimated EIR representing transmission intensity of the areas; 2) the basic reproductive rate (R0) of a non-treated, sensitive infection, which ranges from 1 to 10; 4) Population size; 5) mutation rate or starting frequency of the mutation (1 in 109 to 1 in 1018); 6) initial level of resistance to the partner drug;	The implementation of ACT was cost-effective under different implementation conditions of epidemiology and economic parameters.
Goodman et al (2001)	CQ vs SP	Decision tree	Yes		Dynamics of drug resistance were depicted as	10 years	1) Costs of changing policy per outpatient due to training, health	1) Compliance rate 2) initial ACR 3) Rate of decrease in	This study concluded that with an initial CQ

Study	New drug policy and aims	Modelling type	Resistance considered	Previous modeling work	Model structure	Duration	Economic parameters	Epidemiological parameters	Conclusion & limitations
					a general logistic growth function, The growth rate of resistance to ACT relative to that of current therapies varied		education and regulatory revisions accompanying a change in regimen2) Transport, insurance and delivery as % of drug price3) Outpatient visit costs 4) Inpatient visit costs 5) Average length of inpatient stay	CQ ACR 4) Percentages of non-compliers whom treatment is effective 5) Failure first-line drugs 6) Failure first-line drugs 7) Probability of developing severe malaria after treatment failure 8)Other transition probabilities	resistance of 20%, a delay of 5 years before changing to SP were the most cost-effective strategy
Tediosi et al (2010)	CQ versus ACT	Individual based model of malaria transmission and decision tree model	No	Smith (2006) [186]	The epidemiologic model is a stochastic individual-based simulation of P. falciparum malaria in endemic settings that uses a five-day time step (100,000 individuals)	20 years	1)Treatment seeking behavior 2) Disability weights for neurological sequale 3)Drug cost per course for different age groups 4) Cost of intravenous quinine doses 5) Average length of stay when patient fully recovers or dies	1)EIR 2)Transition probabilities 3)Time point the proportion of vectors become infected at each on a human host	High treatment rates had a proportionately greater epidemiologic impact at low transmission levels.
Pfeil et al (2013) [173]	DHA-PPQ versus AL	Markov model	No		Ma model simulated the progression of malaria disease and probability of recurrent malaria in children in weekly cycles	1 year	DHA-PPQ cost AL cost per course Cost of diagnostic Cost of hospital be day Length of hospital stay	42 treatment failure rates Baseline hazard rate for DHA-PPQ and AL treatment EIR	DHA-PPQ were more cost effective than AL as first-line treatment of uncomplicated childhood malaria across a range of transmission settings in Africa

Application of mathematical model and economic modelling to reduce malaria transmission was pioneered by Goodman in the early 2001. Goodman et al (2001) [182] developed a decision tree model of case management to evaluate the costs and effects of changing from CQ to SP as the first line drug over 10 years, allowing for growth in drug resistance. The primary aim was to determine the optimal time for the drug change. [187]. In this model, the development of drug resistance was a two-step process, the initial emergence of resistance, and its subsequent spread. However, this model only focused on resistance spread, which was caused by the higher reproductive rate of resistance infections in the presence of anti-malarial drugs. To compute the treatment failure, the model incorporated the growth of resistance to CQ over 10 years which was assumed to be 11% and an initial CQ resistance rate of 20%. Once SP was adopted as the first-line drug, the growth of resistance of SP was assumed to be twice quicker than that of CQ resistance due to its long half-life and its widespread use [188]. The health outcome of the model was the number of death, full recovery and recovery with disability determined by the specific compliance and drug efficacy rates.

For the economic assessment of resistance, changing first line drug led to incremental costs from any increase in the costs of new first and second line drugs and the costs associated with the policy change itself due to the revision of treatment guidelines, training staff and education materials. Cost-savings may occur if the new drugs reduced the number of treatment failures; number of uncomplicated and severe malaria cases. Thus the cost-effectiveness results were highly dependent on the initial CQ resistance level, the growth rate of resistance to SP relative to CQ, the time-line of analysis, drug costs, and the cost of policy change. This study concluded that with an initial CQ resistance of 20%, a delay of

5 years before changing to SP were cheapest and averted most DALYs than switching other years. However, this model was simple and did not include many important features in malaria transmissions, such as human population dynamics, seasonal vector dynamics, and elements of the malaria life cycles.

In 2004, Coleman et al (2004)[183] used a Goodman's decision tree model to quantify the cost-effectiveness of using an ACT rather than SP over a time frame of 5, 10, 15 years taking account the growth of resistance to treatments over time. In contrast with Goodman's model, the dynamic spread of drug resistance through time was modified using a logistic growth function. This function was conditional on the initial levels of drug resistance to SP (0.1, 0.3 and 0.5) and ACT drug, plus the maximum possible level of resistance that could not exceed 1 (all the parasite population would be resistant to drug i), and the maximum growth rate of resistance against SP and ACT drug. As for the costs, this study considered only an increase in drug prices between treatment strategies but did not take into account policy change costs as in Goodman. The conclusion is that when baseline ACT resistance frequency was 0.001, the growth rate of resistance of ACT relative to SP would have varied from 1.5 (at a 10% starting level of SP resistance) to 5 (at a 60% starting level of SP resistance) for ACT to be more cost-effective strategy.

In 2004, this year witnessed an increasing support for the wide-scale deployment of ACT. Yeung et al (2004) [184] employed a dynamic model of malaria transmission (compartmental) to evaluate the cost-effectiveness of switching from SP to ACT taking account of the development of resistance. The model assumed a random emergence of resistance for different drugs. A single resistant parasite was capable of expanding and transmitting by the basic reproductive rates (Ro) and

resulted in one or more resistant infections in the next iteration. This rate (Ro) was lowest in sensitive infections that received ACT. This model advances further than Goodman's model because it incorporated immunity function that were constructed based on age stratified rates of infections at different transmission intensities. It is widely known that in low or unstable transmission areas, drug resistance spread rapidly. Population had low immunity thus parasite infections led to acute symptomatic disease which was most likely treated. Therefore, drug resistance transmitted rapidly in low transmission areas due to high drug pressure on existing parasites [189] This situation reversed in high transmission areas. At the end of each model iteration, the total number of infections (resistant and sensitive) were obtained and then fed back into the model so that the next model iteration ran with the updated infection and the immunity profile.

As for the economic assessment of resistance, the incremental costs covered increased cost of drugs using ACTs; The ACT was associated with a decreased incidence in malaria and therefore sustained effectiveness of the combination for more than 10 years. The cost savings from reduced treatment helped to lower the initial high drug cost of ACT. Therefore this study concluded that the implementation of ACT was cost-effective under different implementation conditions of epidemiology and economic parameters.

In the mid of 2013, Spiliotopoulou et al (2013) [179] used the compartmental dynamic model of malaria transmission developed by Boni's work [170] to study the trade-off between risk of drug resistance and operational costs that allowed for treatment with multiple drugs. Specifically, this study weighed against better health outcomes resulting from the treatment with multiple drugs and an increase in

procurement and safety stock holding costs from higher drug variety in the supply chain. This model incorporated immunity to malaria, allowing slow waning and acquisition of immunity for individuals that were infected a long time. Treatment of any single drug sooner or later led to the mutations that conferred drug resistance. The model took account all drug resistant and multi-drug resistant types to the ten drugs in the model (n=1024). Resistant strain to a single drug had a 1% fitness cost of resistance, and an additional 1% fitness cost for resistance was assigned to each additional drug.

As for the economic assessment, the supply chain costs, defined as the sum of procurement and safety stock holding cost, was monotonically increasing in the number of drugs employed simultaneously in the population for a given time period, when demand and procured quantity were regarded as exogenous. Nevertheless, when demand was endogenous, meaning that the current procured quantity of treatments per period was partly determined by the disease prevalence and burden in the last periods, supply chain cost was not necessarily increasing on the number of available drugs because the number of treatment reduced over time as number of drugs increased. This study concluded that multiple drugs in the population were an optimal strategy under a wide range of scenarios other than high drug costs, high volume discount and high disease prevalence.

4.2.2.2 Discussion

Modelling methods for resistance:

This part presents a review of mathematical models that have been used for economic analysis of changing first-line drugs against the malaria taking account of the development of drug resistance. This review found that the most frequently employed health economic modelling techniques to investigate malaria

transmission and resistance dynamics during the year 2000s was decision tree [190,191]. The reasons can be that this type of model was simple to develop and run times were very short and produced quick results [192]. However, such models ignored the basic characteristics of transmission dynamics for example (i) the widespread of infection in a population over time and, (ii) on how the individuals were connected and able to transmit infection to one another through mosquito vectors [193][194].

Dynamic transmission models of malaria (compartmental) have been received more attention since 2010 because they were deemed to produce more realistic results. These types of model tended to focus on whole numbers of individuals channeling through health states and included a degree of random variation depending on the initial conditions of the models [192]. Two studies included the stochastic compartmental model evaluating the impact of alternative interventions on artemisinin resistance ([179,184]). Another study tried to combine decision tree of case management models internally within disease models (Tedios et al 2006 [195]) but did not consider the development of resistance. By incorporating information on intervention costs and cost of illness, transmission models can be used for economic evaluation, thus capturing both the direct and indirect effects of an infectious disease intervention in the evaluation [194] . For examples vaccine can have indirect benefit for the untreated adults intervention due to population-wide reductions in transmission [193]. The reduction in transmission increased over time, leading to lower infection and resistant cases [183,193]. Nevertheless these compartmental transmission model-based studies concluded that they did not include many features important in malaria transmission, such as the explicit vector population, multiple levels of immunity, or the liver or asexual stages of infection,

mosquitoes biting random, seasonal vector dynamics although ttheir conclusions have proven very useful conceptually. In LMICs, a major factor preventing the full integration of modelling in malaria and economics has been quoted as the lack of availability of location-specific data of sufficient quality such as the growth of drug resistance, variation of drug costs over time [192,196] .

Modelling the economics of resistance:

Antimalarial drug resistance had a major impact on health services. The increase of transmission and drug failures led the increase in the cost of medical care. There would be more patient follow-up care, diagnostic tests and even increased costs of new drugs [197]. Some countries might consider changing the drug policy but this change were significantly associated with cost with retraining health care workers, printing new drug regimens, and stocking new drugs[198].

Another cost of artemisinin resistance was the increase in morbidity and mortality in LLMICs [189]. It was estimated that if ACT were failing at a rate of 30%, and treatment of severe malaria with quinine, an excess of 116,000 deaths occurred annually in the scenario of widespread *artemisinin* resistance [199]. The predicted medical costs on a global for retreatment of clinical failures and for management of severe malaria were US$32 million per year and productivity losses of US$385 million for each year during which failing ACT remained in use as first-line treatment[200]. Apart from the cost of case management, the economics of drugs resistance has cost implications on the change of the drug policy and on the supply chain; this is the topic of the next section.

4.2.3 **Costing studies of changing the national single first-line drugs to treat uncomplicated malaria - a systematic review of empirical evidence:**

4.2.3.1 Introduction

In this study, the costs of changing single first-line drugs were defined as the incremental resources, either expended or foregone associated with implementing a new first-line drug in the health system. Based on preliminary reading, there were many different types of costs of implementation and different names were used. The main classification of costs were non-drug costs or "program costs or "non-recurrent" costs which incurred initially at the beginning of the implementation [201], and drug costs or costs recurrent over time. I categorized the costs into 2 main categories to use as the basis for data extraction:

1. Non-recurrent non-drug costs were defined as costs of activities such as training, monitoring and surveillance, consultancy, and revision, and communication which incurred initially at the beginning of the implementation[202].
2. Recurrent non-drug costs were defined as the costs of drug distribution, monitoring, storage, any costs other than drug procurements and treatment costs

This review focused on the non-recurrent non-drug cost of policy change, given the expected difference in the number of times first-line policy would have to be changed in the different strategies. These initial costs are grouped by different program activities and converted to the standardized unit cost per person per year in low and in middle-income countries.

4.2.3.2 Methods

Search strategy and inclusion criteria

I focused on costing studies and costs-effectiveness studies that reported the costs of implementing or changing a national drug policy in low or middle-income countries. Therefore I conducted a systematic search for published and scientific journals in PubMed, Oxford University SOLO databases for the period 1995 to 2015 as well as a manual search of reference lists of all papers. This timeframe is chosen because this is the time that the majority of the replacement of national single first-line drugs occurs [203]. Key search of text terms used in any fields (titles, abstracts, and journals) included terms related to "Costs AND changing OR switching OR implementation AND first-line drugs OR drug policy AND malaria" (Appendix 12).Costing studies from randomized clinical trials and review articles were excluded.

A preliminary search in the PubMed resulted in a very limited of studies that reported the costs of changing drug policy or single first-line drugs. I expanded the search strategy in Google Scholar to include published national malaria reports that provided the estimated budget for the change of national antimalarial drug policy during the implementation years. This was a broad search engine type search that lacked many of the features and functionality of specialist subject databases. Additionally, I collected published Vietnamese national malaria reports dated from year 2000 to year 2015 not online but from the National Institute of Malaria, Parasitology and Entomology. The search strategy is summarized in Figure 4-1.

Data extraction

The main characteristics of each article were collected with regards to the year of publication, the country origin of the data, target population at risk, interventions and comparators, duration of transition time, year of costing and discounting, setting/scenarios, sensitivity analysis. Additionally, I captured the methodological

approach of these studies regarding how costs of the changing single first-line drugs were estimated. Specifically, information on how authors measured non-drug costs other than drug purchases was extracted.(i.e., assumed or measured), and finally the monetary value of the incremental on-drug costs in terms of cost per person at risk per year, and the cost structure of non-drug costs by activity.

Data adjustment and analysis

After the data extraction, 1) I adjusted the total cost of policy change to the standardized cost "per population at risk per year" to facilitate the comparison of findings across a wide range of settings, disease areas under the same unit of measurement. To estimate standardized costs of policy change, the total costs by activity component were averaged by the target population at risk and the time period that it took to achieve the effective roll out.2) Data synthesis and discussion: The data extraction was stratified by South East-Asia or Sub-Saharan Africa countries. The data were also classified according to types of policy changes from inexpensive drug-CQ to inexpensive drugs-SP or inexpensive drugs-CQ or SP to more expensive drug-ACT. Mean cost analysis was carried out for both groups.

The methodology used to adjust the costs in the identified studies to 2013 USD equivalent was as follows. The costs of the interventions surveyed in this review were extracted from studies evaluating costs in a range of international currencies over a period of time dating back to 2000. For meaningful comparisons between costs from different studies to be made, costs were adjusted to a common year and a single currency.

Costs of interventions were first converted from US dollars to local currency using the exchange rate at the year of costing in these studies. All these costs were then

inflated to 2013 prices via the local consumer price indices (local currency inflation rates) and then converted to 2013 USD using the 2013 U.S dollars exchange rates. The local consumer price indices and U.S dollar exchange rates were obtained from the World Bank to allow comparability among countries. This method of inflating and converting the costs of interventions is appropriate for internationally traded goods such as antimalarial drugs and was used in a number of studies investigating the cost and cost- effectiveness of key malaria control interventions [204]. These costing studies will provide the evidence base for the cycling/sequential cost assumptions in Chapter 5.

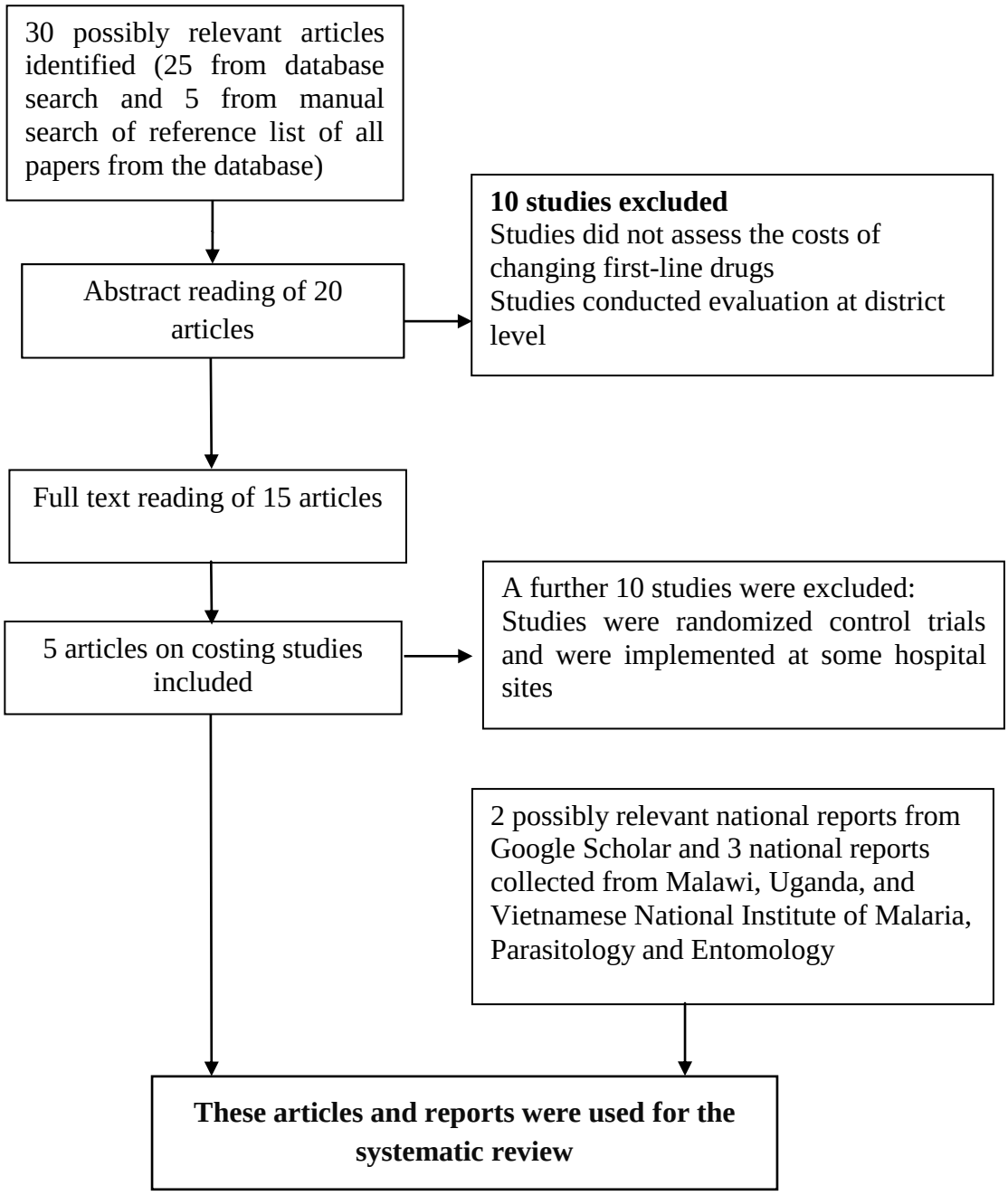


Figure 4-1: Flow chart of search strategy for the costs of changing first-line drugs

4.2.3.3 Results: Costs of changing single-first line drugs treat uncomplicated malaria

Figure 4.1 shows the number of articles identified at each step of the review process. The searches of PubMed, Oxford University SOLO and Google Scholar database produced 15 individual peer review articles being fully reviewed using the data extraction matrix. Our results show that a very few studies consider some incremental non-drug costs in addition to drug procurement. In 10 of those 15 studies the authors did not consider incremental non- drug costs of the changing single first-line drugs. Ten papers were excluded after full-text reading because they assessed the cost of changing first-line drugs within randomised controlled trial and therefore these studies only considered the changes in healthcare costs.There were 3 articles that reported non-drug costs on the policy change CQ to SP and 2 studies on SP or CQ to ACT evaluation were identified. We also found 5 national reports provided the incremental budget to assist the policy change during these years and the years post policy change. Most national reports evaluated the SP to ACT (Table 4-3 Table 4-4 and Figure 4.3 by the end of this chapter).

The first study by Goodman and colleagues [181] captured the evaluation of 1995 policy change from chloroquine to SP in Malawi, which estimated the nationwide non-drug costs of implementation at $575,514 (1995 USD) for a transition period lasting 5 to 10 years, giving the annual non-drug cost between $0.01 and $0.02 (2013 USD) per outpatient. These estimates were lower than the non-drug cost estimates of the evaluation of the 2001 policy change from chloroquine to SP in Tanzania from Abdulla and colleagues [205] that were prepared for the Commission on Macroeconomics and Health which gave the total non-drug costs

of $424,204 (1999 USD) for over 3 years of implementation and non-drug cost per person per year was $0.02 (2013 USD) (33 million population at risk in 2002). The higher cost estimate was because Abdulla study included the costs of management strengthening in cost analyses; meanwhile the study in Malawi neglected this cost.

A later study, Mulligan and colleagues [198] conducted the evaluation of the 2001 policy change from CQ to SP under real life conditions, which estimated nationwide non-drug costs of implementation at $813,743 (2001 USD) over 3 years, giving the non-drug cost per person at $0.03 (2013 USD). Here one thing to note is that in the prospective costing of the CQ to SP switch by Abdulla and colleagues, although carefully done, the non-drug cost estimates were approximately half of what was actually spent in real life implying that the cost of policy change may often be underestimated in the planned state and better evidence of costs of policy change should be highlighted. By far, the largest cost component was the training of health workers on the new policy.

The incremental non-drug costs of switching from CQ to SP tend to be higher than the cost of SP to ACT. For example, the non-drug costs of switching from SP to ACT in Composite Scenario IV were 10 times higher the costs of switching from CQ to SP at 10,143,000 (2003 USD) [197], giving the incremental non-drug costs person at risk of $0.15 (2013 USD).Using the costs associated with deploying ACT in one Rufiji district, the costs were extrapolated to estimate the nationwide costs of the policy implementation in Tanzania in 2003. Four methods were used for extrapolating the district costs to the national level :i) the variable costs were scaled up by the number of districts; ii) the variable costs were scaled up by population; iii) the number of cases and associated drug costs were scaled up by malaria outpatient diagnoses, or iv) a composite method: the training costs of Rufiji district

were scaled up by the number of health facilities in Tanzania, the drug purchase costs were scaled up by the number of malaria outpatient diagnoses per year in Tanzania, and the communication and publicity were scaled up by the total population in Tanzania.

Njau and colleagues[197] found that the non-drug costs associated with the change of single first-line drug from SP to ACT over 3 years was estimated at $10 million (2003 USD) in the composite method, $5 million to $15 million for different scenarios, giving the cost per person per year of **$**0.15 in the composite method, and $0.08 to $0.2 (2013 USD) in other scaling-up methods. Most of the incremental costs were communication and publicity (70%) and monitoring (12%). The non-drug costs of policy changes from SP to ACT were 10 times higher than the policy changes from CQ to SP because the costs calculation was based on intensive data collection at the district level regarding the delivery of the ACTs during the period of transition. On the other hand, Mulligan and colleagues estimated the cost of the policy change at the national level.

Taking account of implementation strategies, a study set in Cambodia focused on evaluating specific interventions that would enhance the widespread use of the new single first-line drug (artesunate and mefloquine) in 2000 [206]. If the country established the outreach team or village malaria workers (VMW) to assist the policy change, the cost per person with ACT drugs could be double the costs than those without implementing these interventions. The incremental costs of policy change per person per year were increased from $0.69 to $1.51 (+150%) (2000 USD) for VMW scheme and $.044 to $0.67 (+50%) for outreach team.

Five national malaria reports documented their budget to support the change of sin gle first-line drugs. Malawi changed their single first-line drugs from SP to ACT in 2007 [203]. The cost of change was shown in the Malaria strategic plan 2005 to 20 10 that was compiled by the Malawi Ministry of Health[207]. The unit cost of chan ging single first-line drugs was estimated at $0.07 (2013 USD) per person per year after adjusting for the population of 13 million individuals at risk of contracting ma laria in 2007. On the other hands, in Uganda the implementation of the new policy was actually in place in 2006 due to claims of mismanagement. The cost of introdu cing the new ACT in 2006 [208,209] was estimated at $2,740,000 (2006 USD), and the unit cost per person was estimated at $0.13 (2013 USD) for the population of 2 9 million individuals.

Vietnam experienced 3 policy changes of national single first –line antimalarial drugs during the year 2000 to 2011. The first-line drugs were replaced from mono-artemisinin to a combination of dihydroartemisinin, piperaquine, trimethoprim and primaquine (CV8) or artesunate + primaquine to treat falciparum malaria in 2003[210], and then switched to artesunate or CV8 or Dihydroartemisinin-piperaquine (DHA-PPQ) + primaquine in 2007 [211], and to DHA+PPQ + primaquine in 2009 [212]. Prospective costings were available in the Vietnamese national antimalarial reports for the years that incurred the change in treatment guidelines. The total non-drug cost of changing single first-line drugs were recorded at $199,000 (US$2003) in 2003, at $65,060 (US$2007) in 2007 and $265,660 (US$2009) respectively. The first policy change required higher start-up costs than the second and third change. The third policy change was the most expensive as the country devoted more resources to purchase ACT as the national first-line drugs. When adjusting with the population at risk, exchange rate and

inflation rate, the unit non-drug cost of policy change per person was $0.01 (US$2013) in 2003, $0.004 (US$2013) in 2007 and $0.012 (US$2013) respectively. The non-drug costs included activities such as research and regulation meetings (3%), revision and printing treatment materials (4%), training (47%), monitoring and surveillance (26%), and information &education& communication (IEC) (20%) (Figure 4.2).

Figure 4-2 shows the trend of the annual budget for non-drug costs obtained directly from Vietnam's National Institutes for Malaria, Parasitology, and Entomology from year 2001 to 2011. The non-drug cost per person associated with changing single first-line in African countries was higher in African countries than those in Vietnam (Vietnam: $0.009, African countries $0.1) (Table 4-2). The differences in costs were likely due to the broad definition of population at risk in Vietnam which was based on the provinces from where the projected cost estimates per person came from. On other hand, the population at risk from African countries was estimated by geography information system (GIS)[213] which was believed to give more accurate results. Therefore, it was felt that that the population at risk covered in Vietnam should be much lower if taking account of more appropriate measurement.

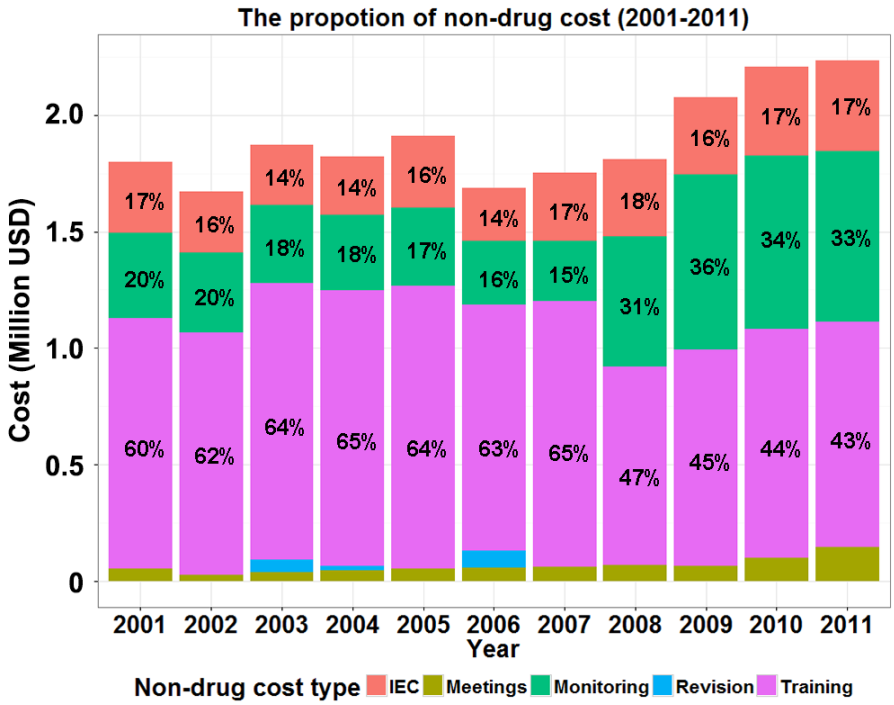


Figure 4-2: The trend of annual Vietnamese malaria budget for non-drug activities (million USD) during the year 2001 to 2011.The proportion of non-drug costs in Vietnamese national malaria budget. The costs in US dollars (y-axis) were plotted against the time (years) from 2001 to 2011. This graph depicts the proportion of the total non-drug costs for Vietnamese population every year which is made up of the consensus meetings (green), revision and printing (blue), training (purple), monitoring (dark green), and communication and publicity (red). The single first-line drugs switched in 2003, 2007, and 2009. The national budget was increased slightly during the year of transition and most of the incremental-non drug costs were attributed to malaria training, surveillance and resistance monitoring.

4.2.3.4 Discussion

This review focused on the approaches to estimate the incremental non-drug costs of introducing national drug policy. Incremental non-drug costs referred to those aside from drug costs and included program activities such as staff training, social mobilization, monitoring, surveillance, and others. Our results showed that very limited studies considered all the non-drug costs in addition to drug procurement. Ignoring the program costs has emerged as an important methodological challenge in this review. Most of studies chose to exclude these costs or these costs could be

included in the treatment costs (Table 4-3). This reflects a failure to capture the true costs and benefits of changing single first-line drugs in costing studies and economic evaluations.

Estimating the non-drug cost of changing single first-line drugs was based on a wide variety of the methodological approaches, which were also a reason for variations in the cost estimates (as seen Table 4-3 and Table 4-4). For example, two studies performed a formal micro-costing evaluation of different program activities [197,198]. Only one study opted for an easy approach by assuming a fixed value for non-drug costs based on Malawi implementation [181]. Earlier studies that estimated the incremental costs associated with changing single first-line drugs from CQ to SP did not consider the costs for monitoring activity and did not explain the reasons why they failed to include these costs. As for the national reports, the incremental budget of introducing the single first-line drugs was not stated clearly. In addition, different countries encountered different operational challenges that led to different cost estimates.

The non-drug costs in the literature may have been underestimated. This is because some studies did not account for the costs of managing stock out rates of ACT supplies. Some studies estimated the overall cost of implementation at the national level, but ignored costs incurred at the lower level of health system. Some studies estimated the costs of the ACT provision through public sector and ignored the private sectors. Overall, these studies have not attempted to measure the broader societal impact of policy change.

In addition to study design variation and limitations, how cost estimates were reported varied widely: some studies reported the cost of policy change as cost per outpatient visit [181] or cost per person/capita [206] or the cost per patient seen and

tested or the cost per Pf patient treated [206]. The majority of articles calculated the costs of policy change based on the questionable duration of implementation. Defining the cut-off point of the policy change is not straightforward, as activities such as additional training courses and community sensitization meetings may have continued long after the official policy launch.

WHO Cost-effectiveness and strategic planning (WHO-CHOICE) has made specific recommendations on how to evaluate costs of implementing national programs. According to these, economic costs of program activities should be considered when performing a CEA to assess the introduction of new programs. However, the present review shows that costs considered in the studies are usually financial costs, only including prices and not considering economic costs. The exclusion of these costs results in an underestimation of the incremental non-drug costs compromising the quality of CEA tools used to support decision for introducing new drugs.

Table 4-2: A review of non-drug costs of changing first-line drugs. The studies are broken down by different drug policies. The cost per person and, or the cost per treated case where available are presented. These studies were undertaken from the health system perspective. The total non-drug costs are illustrated as the currency of the study. Non-drug costs per year per person are presented in 2013 USD. Different scenarios of costing were showed for two studies [197] and [206].

First author, Year, Reference	Drug policy	Costing year	Duration (years)	country	Population at risk	Total non-drug costs (study currency)	Non-drug costs per year per person adjusted to 2013 USD	Study limitation
Goodman 2000 [181]	CQ to SP	1995	5	Malawi	3,800,000	575,514	0.02	Unclear transition time, This study did not specify the costs monitoring
	CQ to SP	1995	10	Malawi	3,800,000	575,514	0.01	
Abdulla 2000 [205]	CQ to SP	1999	1.5	Tanzania	33,000,000	424,204	0.02	Unclear transition time No scenario analysis
Mulligan 2001 [198]	CQ to SP	2001	3	Tanzania	33,000,000	813,743	0.03	Unclear transition time No scenario analysis
Njau 2005 [197]	SP to AL (variety)	2003	3	Tanzania	33,461,849	10,143,000	0.15	Using district costs to estimate the nationwide costs
	SP to AL (districts)	2003	3	Tanzania	33,461,849	9,838,887	0.15	
	SP to AL (population)	2003	3	Tanzania	33,461,849	14,602,827	0.22	
	SP to AL (outpatients)	2003	3	Tanzania	33,461,849	5,170,697	0.08	
	SP to AL (strengthening)	2003	3	Tanzania	33,461,849	11,007,078	0.17	
	SP to AL (increased utilization)	2003	3	Tanzania	33,461,849	10,549,448	0.16	
	SP to AL (cheaper ACT)	2003	3	Tanzania	33,461,849	10,549,458	0.16	
Malawi 2007 [207]	SP to ACT	2007	1	Malawi	13,000,000	1,127,392	0.07	Unclear costing methods

Uganda 2006 [208,209]	SP to ACT	2006	1	Uganda	29,000,000	2,740,000	0.13	Unclear costing methods
Vietnam 2003[210]	CQ to CV8 or artesunate primaquine	2003	1	Vietnam	38,619,387	199,000	0.01	Unclear costing methods
Vietnam 2007 [211]	CV8 or DHA-PPQ	2007	1	Vietnam	26,063,406	65,060	0.004	Unclear costing methods
Vietnam 2009 [212]	DHA-PPQ	2009	1	Vietnam	26,566,219	265,660	0.01	Unclear costing methods
Yeung 2008 [206]	SP to Artesunate-mefloquine (outreach-fixed costs only)	2000	1	Cambodia	19,029	8,385	0.81	This study did not focus on other operating costs, apart from the costs of scaling up interventions to assist the policy change
	SP to Artesunate-mefloquine (village workers, fixed costs only)	2000	1	Cambodia	100,000	68,858	1.27	

Table 4-3: Components of non-drug costs by different program activities. All costs are in 2013 USD. This table illustrates the reviewed studies, the non-drug costs for each program activity, the percentage cost of each program activity (%), and the total non-drug costs per person per year are presented. The average non-drug costs were calculated for African countries, and Vietnam for different types of policy changes. The absolute change in costs from CQ to SP relative to SP to ACT were also computed.

Reference	Current drug policy to new drug policy	Country	Consensus building		Revision and printing		Training		Monitoring		Communication		Non-drug costs per person per year (2013 USD)
			Cost per person per year	%	Cost per person per year	%	Cost per person per year	%	Cost per person per year	%	Cost per person per year	%	
Goodman 2000 [181]	CQ to SP	Malawi	0	0	0.004	17.0%	0.0166	70%	0	0	0.0031	13%	0.024
	CQ to SP	Malawi	0	0	0.002	17.0%	0.0083	70%	0	0	0.0015	13%	0.012
Abdulla 2000 [205]	CQ to SP	Tanzania	0.0010	5.0%	0.0005	2.5%	0.0092	46%	0.0068	34%	0.0024	12%	0.020
Mulligan 2001[198]	CQ to SP	Tanzania	0.00009	0.3%	0.00010	0.3%	0.0049	16%	0.0037	12%	0.0213	71%	0.030
Njau 2005 [197]	SP to AL (variety)	Tanzania	0.0005	0.3%	0.001	0.3%	0.0250	16%	0.0189	12%	0.1088	71%	0.153
	SP to AL (districts)	Tanzania	0.0004	0.3%	0.001	0.3%	0.0242	16%	0.0183	12%	0.1056	71%	0.149
	SP to AL (population)	Tanzania	0.0007	0.3%	0.001	0.3%	0.0360	16%	0.0271	12%	0.1567	71%	0.221
	SP to AL (outpatients)	Tanzania	0.0002	0.3%	0	0.3%	0.0127	16%	0.0096	12%	0.0555	71%	0.078
	SP to AL (strengthening)	Tanzania	0.0005	0.3%	0.001	0.3%	0.0271	16%	0.0205	12%	0.1181	71%	0.166
	SP to AL (increased utilization)	Tanzania	0.0005	0.3%	0.001	0.3%	0.0260	16%	0.0196	12%	0.1132	71%	0.159
	SP to AL	Tanzania	0.0005	0.3%	0.001	0.3%	0.0260	16%	0.0196	12%	0.1132	71%	0.159

Reference	Current drug policy to new drug policy	Country	Consensus building		Revision and printing		Training		Monitoring		Communication		Non-drug costs per person per year (2013 USD)
			Cost per person per year	%	Cost per person per year	%	Cost per person per year	%	Cost per person per year	%	Cost per person per year	%	
	(cheaper ACT)												
Malawi 2007[207]	SP to ACT	Malawi	0	0	0.001	1.0%	0.0554	79%	0.0140	20%	0	0%	0.070
Uganda 2006 [208,209]	SP to ACT	Uganda	0	0	0	0	0.0664	50%	0.0531	40%	0.0133	10%	0.133
Vietnam** 2003[210]	CQ to CV8 or Artesunate primaquine	Vietnam	0.0003	3%	0.001	10%	0.007	70%	0.0012	12%	0.0005	5%	0.010
Vietnam 2007[211]	CV8 or Artesunate primaquine to CV8 or DHA-PPQ	Vietnam	0.0001	2%	0.0001	2%	0.0005	12%	0.0004	10%	0.003	74%	0.004
Vietnam 2009[212]	CV8 or DHA-PPQ to DHA-PPQ	Vietnam	0.0002	2%	0.0002	2%	0.0014	12%	0.0086	72%	0.0014	12%	0.012
Average cost for Africa			0.0003	0.7%	0.001	3.2%	0.0260	35%	0.0162	15%	0.0663	53%	0.106
Average cost for Vietnam**			0.00016	2%	0.00016	2%	0.00096	12%	0.00452	41%	0.00173	43%	0.008
Average cost of policy change from CQ to SP			0.0002725	1%	0.0017	9%	0.010	51%	0.0026	12%	0.0071	27%	0.0214
Average cost of policy change from SP to ACT[1]			0.0005	0.3%	0.0005	0.3%	0.0253	16.3%	0.0191	12%	0.11	71%	0.155
Percentage change in cost from CQ to SP relative to SP to ACT			71%		-71%		160%		628%		1456%		625%

[1]The average costs of 7 scenarios in a Tanzania study (Njau 2005 [197])

* The cost of changing from a monotherapy (CQ) to a combination therapies (CV8 or artesunate primaquine)
**The average cost of changing from a drug combination therapy (CV8 or DHA-PPQ) to another drug combination therapy (DHA-PPQ) in Vietnam 2007 and 2009. The change of drug policy in 2003 from a monotherapy to a combination therapy required more time to revise the guidelines and train the staff. On the other hand, the change of drug policy in 2007 and 2009 took more investment in EIC activities and monitoring the efficacy of drug combination therapies.

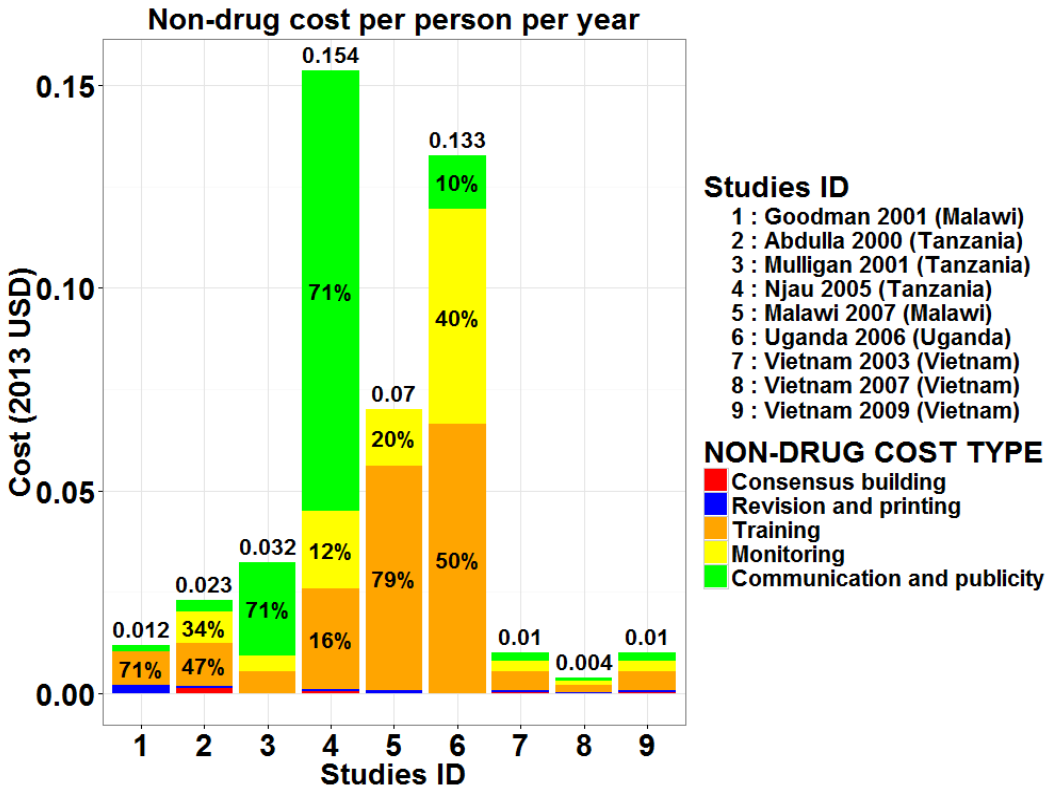


Figure 4-3: The components of the non-drug costs per person per year for different reviewed studies. The costs in US dollars (y-axis) were plotted against the study ID which corresponds to different studies shown in the right-hand legend. This graph depicts the proportion of the non-drug costs per person per year which was made up of the consensus building (red), revision and printing (blue), training (orange), monitoring (yellow), and communication and publicity (green).

4.2.4 **A literature review of the costs of procuring and delivering ACTs**

4.2.4.1 Introduction

This second systematic literature review focuses on the production cost of ACTs and the costs of retail sector distribution chain for malaria treatment. The price for ACT includes the selling price of the producing country, the cost of transporting goods to a country plus freight and insurance (c.i.f costs) if the ACTs are an imported good, and the costs of transporting and distributing goods within a country (domestic margin/local mark-up).

Search strategy and inclusion criteria:

I focused on studies that provided the estimates of the cost of purchasing ACT, the ACT retail prices, and wholesale- and retail-level price mark-ups in developing countries. I conducted a systematic search for published and scientific journals in the PubMed database for the period 2000 to 2015. Key search of text terms used in any fields (titles, abstracts, and journals) included terms related to “Costs” AND “drug” AND “delivery” AND “supply chain” AND “first-line drugs”. The search strategy is summarized in Appendix 13.

Data extraction and data analysis: I collected the main characteristics of each article including the year of publication, the country origin of the data , interventions and comparators, year of costing and discounting, setting/scenarios, the cost of purchasing ACT, the ACT retail prices, and wholesale- and retail-level price mark-up and any sensitivity analysis was conducted.

4.2.4.2 Results:

The searches of PubMed yield 351 studies and 6 individual peer review articles being fully reviewed.

The production costs of ACTs: Firstly this review explored the different production costs of ACTs. The prices per treatment course of AL were $0.43 and $0.83 for children receiving 20/120mg and 6 times 40/120mg of AL[172]. The DHA-PPQ prices per course of oral treatment were 0.66 and $0.93 for children receiving 3 times 20/160 mg and 3 times 40/320 mg DHA-PPQ tablets (Global Fund 2013). These ACTs were 10 times more expensive than conventional antimalarial medicines. The high price of the ACT was driven mainly by the cost of the *artemisinin* derivative. The high costs of *artemisinin* (the ex-manufacture prices) were due to the long (14-month) production cycle. These plants must first be cultivated and harvested and the drugs then extracted and processed rather than simply synthesized from inexpensive chemicals. Artemisinin are the sweet wormwood plant mostly grown in China and Vietnam which provides 70% and East Africa 20% of the world's raw plant material.

Factors affecting the cost of producing ACTs: The production cost of ACT could be higher or lower depending on the brand & delivery channel, contract volume and competition. Danzon and colleagues [215] identified the main determinants driven the ex-manufacturer prices for originator and generic drugs to treat HIV/ADIS, TB and malaria in middle and low-income countries (MLICs). They were: i) Brand and channel effects: The differentials of the ex-manufacturer priceswere31.6% cheaper for retail generics, -42.4% for tendered originators, and -66.8% for tendered generics relative to the retail originators for the countries with matched price per capita. Therefore, the producer's competitive tendering significantly lowered the procurement prices. ii) The elasticity of price with respect

to volume was -0.106, indicating that if the volume increased 1%, the price would have reduced 10.6% of its value. However contract volume weakly contributed to lower procurement prices mainly for originator. iii) As for the effects of the competition on the price, the marginal effect of an additional tendering generic was to reduce drug prices by 4.5% compared with only -0.89% for an additional retail generic drug. Historical experience demonstrated that the prices of ACTs was likely to decrease over time as more producers and competition were encouraged and economics of scale were achieved[216].

The percentage mark-up for the imported ACTs (c.i.f mark-up): Apart from the costs of manufacturing the drugs, the price of the drugs also covered the freight costs, clearing charges, and any taxes if the drugs were imported from overseas. The c.i.f mark-up for traded goods across selected countries in different regions were in the range of 16% (in Denmark) to 71% (in Afghanistan), with a median mark-up of 28% of the drug price [217].

The percentage mark-up for local distribution of ACTs:

The wholesale percentage mark-ups on ACTs varied by country. The price mark-up of antimalarial drugs channeled from manufacturer to consumer through the usual public and private sectors were estimated at13% in Senegal, 20% to 30% in Zambia, and 1.82% to 49.57% in Cambodia, while the private pharmacies add margins of 9.9% to 56.2% in Senegal, 30% to 40% in Zambia, and 1.85% to 2300% in Cambodia. High price mark-up in Cambodia because the drugs went through many system levels to get to the consumers.

A recent study [218]found the costs of routine delivery of single first-line drug ACT within the public sectors from the central level to peripheral levels in Benin

and Kenya in 2013 added $0.2011 (SD=0.1216) and $0.2443 (SD=0.0183) to the acquisition cost per treatment course of ACT in Benin and Kenya (normalized to USD 1) respectively. Therefore total supply chain cost accounted for approximately 20 to 24 percent of the initial acquisition costs in the public sectors in Benin and Kenya. Each cost item contained the labour, utilities, security, maintenance, insurance, depreciation. These costs were highly sensitive to product volumes.

Palafox and colleagues [219] found that the public wholesaler mark-ups were the lowest,11% to13%, in DRC and 14% to 20% in Uganda followed by Nigeria 15% to 30% and Zambia 25% to 31% and highest in Benin 31% to 36% and Cambodia 41%. Retailer's mark-ups were higher ranging from 22% in Nigeria to 71% in Zambia. ACTs were produced by domestic manufacturers in the DRC, Nigeria, and Uganda; however none of these products was prequalified by the WHO at the time of data collection. The retail price per adult treatment doses for ACT tablets were lowest in Cambodia ($US1.18) followed by the DRC, Nigeria and Uganda ($4.03 and $4.26) and highest in Benin ($7.50 and Zambia $8.90). Retailer's mark-ups were higher ranging from 22% in Nigeria to 71% in Zambia. This study classified factors that affected wholesalers and retailer's drug pricing decision: i) Operating expenses such as supplier prices, the costs related to the transporting goods, staff salaries and the costs of maintaining premises and licences, ii) Product availability and characteristics such as domestically produced antimalarial offer lower mark-up than imported products, iii) Discounts and price discrimination for example, wholesalers and retailers commonly used discounts based on order volume or regular or long-term customers.

The effects of multiple drugs policy on the distribution of antimalarial drugs: A study [179] evaluated the operational costs when using multiple drugs to treat malaria. This study found that increasing variety of distributed drugs led to higher cost of procuring the drugs and higher inventory holding costs (or storage costs). One of the reasons for this was because volume discounts were a common practice in the pharmaceutical sector, implying that using more types of drugs for specific disease resulted in a higher per unit price for the sourced drugs. This study assumed a range for the volume discount of 0.1%, 1%, and 10% for 100,000 units. The fixed cost of ordering per supplier per period was $1000. Another reason was that when demand was not certain, wider drug variety for a specific disease would lead to higher safety stocks and therefore higher inventory holding costs as demand volatility for each drug increased with drug variety. This finding was based on standard inventory theory stated that total holding and stock out costs were higher when demand was not aggregated for one-period setting.

4.2.4.3 Summary on the costs of producing and delivering the ACTs:

This review found that the median retail price for ACTs ranged from $1.18 (Cambodia) to $8.90 (Zambia) per adult treatment. Going into specific drugs, the ASAQ was priced at $1.35 to $1.55 per adult dose; AL was $2.40 per treatment course. If the drugs were imported from overseas, the c.i.f percentage mark-ups are approximately 28%. The public wholesaler percentage mark-ups on ACTs tablets were lowest ranging from 11% -13% (the DRC) and highest at 41% (Cambodia) on purchase prices while the private retailer percentage markup on ACTs tablets could be over 59% (Table 4-5).

There were a wide range of factors that influence antimalarial prices such as the contract volume (this was found to reduce the price by 31.6% to 66.8%), and additional competitors (reducing the price by 10.6% for an additional competitor). However the price of ACTs was expected to decline over time under an agreement with WHO, the manufacturers sold the ACTs to developing country governments and international donors at a non-profit basis which is set to recover the cost of production; in exchange, they relied on WHO to provide demand forecasts because the long production cycle coupled with a very short shelf life of only 24 months makes the accurate demand forecasts difficult.

Overall, studies tended to focus on the distribution chain serving a single type of outlet such as pharmacies. Studies were generally descriptive and provided limited evidence on volume stocking or costs at intermediate levels. A better understanding of the antimalarial distribution chain on the drug price is urgently needed to provide the evidence base for cost-effectiveness analysis.

4.2.5 **Conclusions of chapter 4:**

This literature review produced a range of estimates for the costs of changing first-line drug policy, and the full production and distribution costs for ACTs, both of which will feed into the economic evaluation in the next chapter. The review also suggests that changing the new single first-line drugs has been evaluated less rigorously than warranted. In addition, there is considerable variation in the costs of ACTs between and within countries that should be better acknowledged in economic evaluations.

Table 4-4: Review of drug costs of *artemisinin* combination therapies (ACT) studies (Currency: 2013 US dollars) and the percentage mark-up for delivery of the ACT

Reference	Intervention	Costing year	Country	Costing method	Unit costs or percentage change in price (%)	Determinants of variance in prices
ACT drug prices per adult dose						
Palafox (2015) [219]	ACT retail prices	2009 - 2010	Benin Cambodia Congo Nigeria Uganda Zambia		$7.50 per adult dose $1.18 $4.03 $4.26 $4.26 $8.90	
ACT supply chain (percentage mark-up) from central level to the health facilities level						
Johns 2003 [217]	Percentage mark-up for freight (cif)	2003		The freight costs, clearing charges, and any taxes	28% (16% to 71%)	
Shretta & Guimier 2003 [220]	Percentage mark-up for local distribution	2003	Senegal Zambia Cambodia Senegal Zambia Cambodia	Public wholesalers Retailers in the private sector	13% 20% to 30% 1.82% to 49.57% 9.9% to 56.2% 30% to 40% 1.85% to 2300%	
Shretta 2013[218]	Percentage mark-up for local distribution	2013	Benin Kenya	Supply chain costs from central level to health facilities	20% or $0.2011 (SD: 0.1216) 24% or $0.2443 (SD: 0.0183)	Product volumes Labour Utilities
Palafox et al 2015	Percentage make-up for	2009 - 2010	Cambodia Congo	Public wholesalers	31% to 41% 11% to 13%	i) Operating expenses such as supplier

Reference	Intervention	Costing year	Country	Costing method	Unit costs or percentage change in price (%)	Determinants of variance in prices
	local distribution		Nigeria Uganda Zambia 6 countries	Retail wholesalers	15% to 30% 14% to 20% 25% to 31% 22% to 71%	prices, transport costs, staff salaries ii) Price competition iii) Product availability and characteristics
Danzon 2015 [215]	Factors reduced the ACT prices	2015	MLICs	-35.1% price differentials between retail originators and retail generics The average elasticity of price with respect to volume is -0.106 (-) 0.89% for an additional retail generic to (-) 4.5% for an additional tendering generic		Brand and channel Contract volume Competition

Chapter 5

Economic evaluation of malaria multiple first line therapies

5.1 Background of the study and the objective of this chapter

Artemisinin resistance has become a threat to public health in South East Asia. One of the strategies to slow artemisinin resistance might be the introduction of multiple first-line drugs (MFT). Our research in Vietnam [63] used an individual-based microsimulation of *Plasmodium falciparum* malaria that compares three different treatment strategies at national level to examine which strategy can be applied as widely as possible without accelerating the erosion of drug efficacy by drug resistance. The three strategies include the "Cycling strategy", defined as a national first-line drug policy that changes every 5 years. "Sequential strategy", where the national first-line drug policy changes every time the percentage of treatment failures reaches 10% in the population with an assumed 1-year delay. The number of policy changes will be obtained from the IBM model. The third "MFT strategy" is defined as one where multiple first-line drugs are distributed at once in the population and no policy change occurs. There are a number of ways the MFT strategy could be implemented. The 'ideal scenario' of the MFT is where drugs are equally distributed to individual patients in a randomized manner within shops, clinics and hospitals. This MFT strategy, however, is unlikely to be implemented in real life, as the logistical demands will probably result in poor compliance. The public/private method is another alternative approach but it has a major limitation in that the MFT strategy will fail in places that are mostly private or majorly public sector.

The WHO recommends that cost-effectiveness of new intervention should be established before strategies are recommended as policy. The objective of this chapter therefore is to assess the long-term costs and cost-effectiveness of an MFT strategy as compared with either sequential or cycling policies. Predictions for malaria incidence and mortality under the different strategies were generated using a pre-existing dynamic stochastic simulation model of the epidemiology of *Plasmodium falciparum*. These simulated outputs fed into an economic model, which along with the previously estimated costs of changing drug policy and those for distributing ACTs under the different strategies produced the incremental costs and health gains (converted in to DALYs averted) of implementing the MFT strategy as compared with single first-line therapies. The analyses were run for different scenarios of *P.falciparum* biology and epidemiology, to approximate the impact of MFT in low and high transmission settings.

5.2 **Methods**

5.2.1 **Epidemiological and case management model**

To predict the cost–effectiveness of the MFT strategies, I employed a dynamic, individual-based, stochastic model of *P.falciparum* malaria (OUCRU-IBM model) under different epidemiological scenarios. The epidemiological model has been described in detail elsewhere [221] and the rationale of the model relied on this study [170]. Briefly, the OUCRU IBM was run for 20 years and consisted of 1 million individuals of all ages. This model included individual–level host detail, age-specific immune acquisition, biting rate heterogeneity, drug-specific pharmacodynamics, host parasite density modelling, and multiplicity of infection and recombination. The OUCRU IBM included a case management model for each individual as portrayed in Figure 5-1. The case-management model estimated the

impact of different treatment strategies on the health outcomes of parasitological cure, full recovery, or death. For each strategy, adults and children first developed uncomplicated clinical malaria. A proportion of clinical cases received treatment with probability (P1), and others were left untreated. P1 was set as the treatment coverage that ranged from 50% to 90%. For treated cases, there was a probability (P2) that uncomplicated malaria case experienced treatment failure. Effective treatment indicated that the individual adult/children had cleared the parasites on their 28th day of assessment was defined as adequate clinical response using the WHO criteria, and treatment failures indicated otherwise. Treatment failure was defined as i) failure to clear parasitaemia or ii) recrudescence within the 28 day follow-up period. This number is the product of the probability of drug resistance to each drug under different strategies and the estimated proportion of patients who received treatment. For untreated cases, the model assumed that most individuals were able to recover subjected to natural clearance due to host immunity, and a minority died with probability (P3). The OUCRU IBM model set the mortality rate for untreated malaria (P3) to 4% for age-group 0-1, 2% for age group 2-5, 0.4% for age-group 6-10 and 0.1% for older age groups. These mortality rates were obtained from the published literature review. This decision tree also assumed the same mortality rate as the OUCRU IBM model. The data inputs contained the population size, the number of treated cases for each drug, the number of treatment failures for each drug at day 28, the number of death, the number of the malaria related mortality, the number of untreated cases (Table 5-1). The data were obtained annually for each strategy across different age groups over 20 years.

Figure 5-1: Case management decision tree from OUCRU Malaria IBM. Transition probabilities are shown below each path and are derived from data drawn from OUCRU IBM.

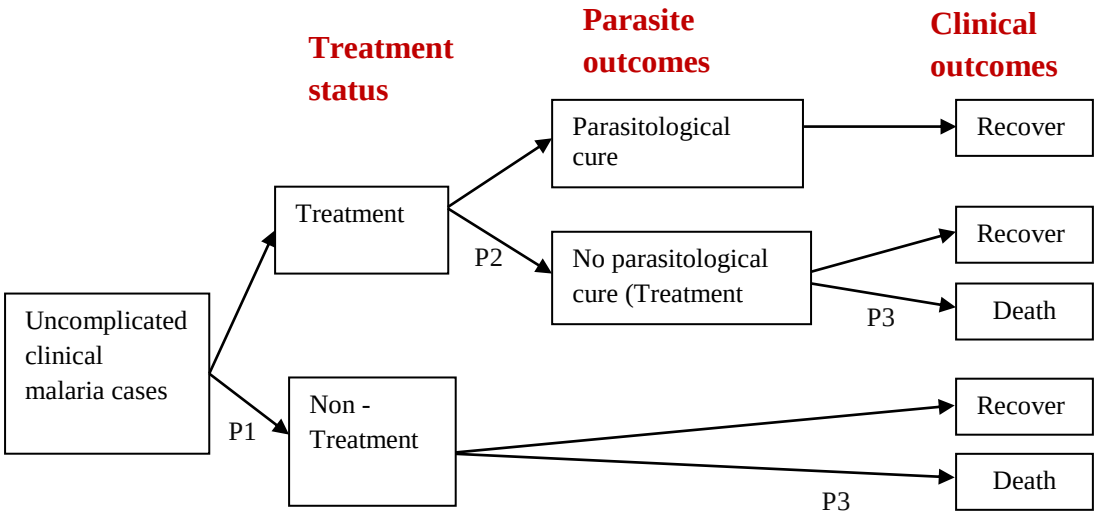


Table 5-1: Simulated outputs from OUCRU IBM model

Notation	Description	Data obtained from OUCRU IBM
P1	Treatment coverage	Annual number of treated cases for each drug. The annual number of untreated cases
P2	The probability of treated cases progressing to treatment failures (%).	Annual number of treatment failures for each drug / The annual number of treated cases for each drug This probability were calculated annually every year for 80 different age groups by strategy over 20 years
P3	Mortality rate progressing from untreated cases were assumed the same as the mortality rate progressing from unsuccessful treated cases.	The annual number of deaths for untreated cases = The annual number of deaths for unsuccessfully treated cases. These annual mortality rates were approximated as: 4% for age group 0-1 2% for age-group 2-5 0.4% for age –group 6-10 0.1% for older age groups

The OUCRU IBM model, however, was not designed to produce simulated outputs for the number of patients with severe malaria, a key determinant in the costs and effects of different treatment strategies. To assist the cost-effectiveness study, a modified version of the decision tree for case management was developed to quantify the health impact of malaria, including clinical cases of uncomplicated and

severe malaria, as well as associated mortality (Figure 5-2). The modified case-management model included the probability of developing severe malaria progressing from treated or untreated uncomplicated malaria, plus the probability of seeking healthcare for severe cases, and the mortality rates for severe malaria cases. The case –management model was based on the following assumptions:

- Malaria cases were quantified as the number of new infections annually, and assuming these can obtain effective antimalarial treatment (an ACT) only from the public sector. We developed a model of how such care might be delivered in low and high transmission if primary healthcare workers could provide the bulk of care. This setting is entirely realistic in Vietnam because ACTs are unavailable in the private sector. This is of course a huge limitation in most settings where a large number of cases are treated in the private sector.
- Our model assumed that all patients suffering from malaria present at a primary health facility at the onset of uncomplicated malaria. The severe cases upon presentation was ignored as this amounted to 5% of the severe cases that was reported upon presentation in Zimbawe in 2014 [222]
- Effective treatment of uncomplicated malaria was assumed to be cured within 28 days window.
- Severe malaria progressed from untreated and treatment failures of uncomplicated malaria. The model allowed for severe patients returning to inpatients or opt for no further treatment.
- In all the strategies, there was full compliance to treatment guidelines. There were no stock-out problems with the first-line drugs in the public sector.

The decision tree comprised decision nodes with 3 branches for each of the strategies; followed by chance nodes for treatment status, disease status, followed by parasite and clinical outcomes. Firstly, for the treatment branch, the uncomplicated malaria cases presented at formal outpatient facilities, which were hospitals, dispensaries, health centers. For the treatment branch, when first-line drug has failed, the patients either would develop severe malaria with a probability (P3), or continued to suffer from uncomplicated malaria. For uncomplicated malaria cases resulting in treatment failures, there was a proportion of cases (Qi) that either received repeated first-line drugs (AL, DHA-PPQ, or AS-AQ) or received a costlier second-line treatment ($21 per case, 2013 USD). This assumption was based on the actual practice for patients not cured within the 28-day period [174] and these patients are assumed to all recover. As for severe malaria resulting from treatment failures, these cases could either access inpatient care (P5) or not seek treatment. Severe malaria was defined by any of several typical clinical syndromes including high fever with respiratory distress, convulsions, hyperasitaemia, anemic symptoms and neurological disturbances. The mortality of severe malaria cases that did not return for formal care was P6. For the branch of non-treatment, the probability of uncomplicated malaria progressing to severe malaria was assumed at P4. Untreated severe malaria case was assumed to progress in a similar way to failed treatment. These probabilities were then used to generate overall expected costs and DALYs per 1 million individuals for each treatment strategy over 20 years by following the decision tree paths to the end points as shown in Figure 5-2. In order to estimate each of the probabilities in the decision tree, it was necessary to combine estimates from a wide range of SSA countries. For some variables there were simply no data available, so estimates had

to be made following discussions with experts in the field. The probabilities, the ranges used in the modified decision tree and the sources are documented in Table 5-2.

The aim was to assess the long-term costs and cost-effectiveness of a MFT strategy as compared with either sequential or cycling policies using a dynamic stochastic simulation model of the epidemiology of Plasmodium falciparum. The case – management decision tree model inherited the results from a dynamic stochastic model of malaria epidemiology that compared 3 population-level treatment strategies MFT, cycling and sequential developed by Nguyen & Boni (2016) [63]. In the OUCRU IBM model, the authors built a dynamic stochastic simulation of 1 million people, included the individual –level host detail, age-specific effect (age-specific immune acquisition), biting rate heterogeneity, drug-specific pharmacodynamics, host parasite density. The OUCRU IBM model employed a wide range of parameters and their values were randomly drawn from a given distribution to produce a range of health outcomes estimates. On every iteration, the OUCRU IBM model produced the health outcome estimates such as the number of cases, the number of treatment failures, and the number of deaths caused by malaria for each age-group and each year associated with each treatment strategy.

When populating the case-management model, I did not alter the OUCRU-IBM epidemiological models above. The economic decision tree model linked with the malaria epidemiological model by using the outputs of the OUCRU IBM model such as malaria cases, deaths and treatment failures as the inputs combined with the

economic parameters which were also randomly drawn from given distribution to produce results of costs and DALYs.

The health outcome results of the OUCRU IBM model itself reflected a range of scenarios corresponding to different values of treatment coverage (50% to 90%), and fitness cost of resistance (0.1% to 1%) in a low/high transmission setting. Once the OUCRU-IBM model was run, it produced a range of age-specific health outcomes for each year across 9,000 epidemiological scenarios. Based on the results from the OUCRU-IBM model such as the number of malaria cases, I then ran the economic model that I designed to calculate the accumulated discounted costs and discounted DALYs necessary for the implementation of each strategy for each age group for each year across 9,000 scenarios during 20-year period.

I considered this economic decision model as a dynamic model as the input values were updated during 20 years of implementation. The values of the economic parameters and the epidemiological parameters were randomly drawn from defined distributions. By doing the above steps, I hope to have built an economic decision model that has taken account of a wide variety of malaria epidemiological and economic scenarios so that the results can be generalizable to a wide range of settings.

Table 5-2: Parameter values for transition probabilities

Description of parameter	Central value	Lower value	Upper value	Distribution	Reference
P1: The probability of malaria cases of seeking treatment (Treatment coverage) (%)	70%	50%	90%	Fixed value	This is the annual probability that a malaria case would receive treatment from a health facility, arbitrarily categorized as 50%, 60%, 70%, 80%, 90%.
P2: The probability of treated cases progressing to treatment failures (%)	Simulated outputs from IBM for each of the strategies.			Fixed value, determined by strategy and epidemiological setting.	This is the probability that is calculated based on the number of treatment failures for each drug divided by the number of treated cases for each drug across 80 different age groups. These two data sets were obtained from OUCRU IBM.
P3: Early treatment failures lead to severe malaria (%)	2%	0.5%	5%	Beta distribution (α=3 β=156)	Lubell et al 2010 [200]
P4: The probability of untreated malaria case progressing to severe malaria (%)	30% in low transmission	10%	58%	Triangle distribution	This probability is taken from Delphi results for low and high transmission intensities cited from [190]
	13% in high transmission	7%	30%		
P5: The probability of severe malaria patients obtaining inpatient care (%)	48%	19%	88%	Beta distribution (α=5.630 β=5.470)	Maire et al (2011) [223]
P6: The probability that a severe patient that does not return for formal care will die (%)	75% (Low transmission)	40%	90%	Beta distribution (α=7 β=3)	Mortality rate of untreated severe malaria in Asia and South Africa Lubell et al 2010 [200]

Description of parameter	Central value	Lower value	Upper value	Distribution	Reference
	50% (High transmission)	40%	90%	Beta distribution (α=5 β=5)	
P7: Mortality rate of patient with severe malaria attending an inpatient facility dies (%), or Mortality rates of untreated severe malaria	(Annual number of death -D1 –D2) / (IC1 +IC2)			Fixed value	Total number of deaths were obtained OUCRU IBM
Treatment seeking for uncomplicated malaria					
Qi: The proportion of recipients that fail first-line stay as uncomplicated malaria and receive repeated dosage; otherwise receive the second-line treatment	20%	40%	60%	Beta distribution	Chanda et al (2007) [174] Mori et al (2015) [175]

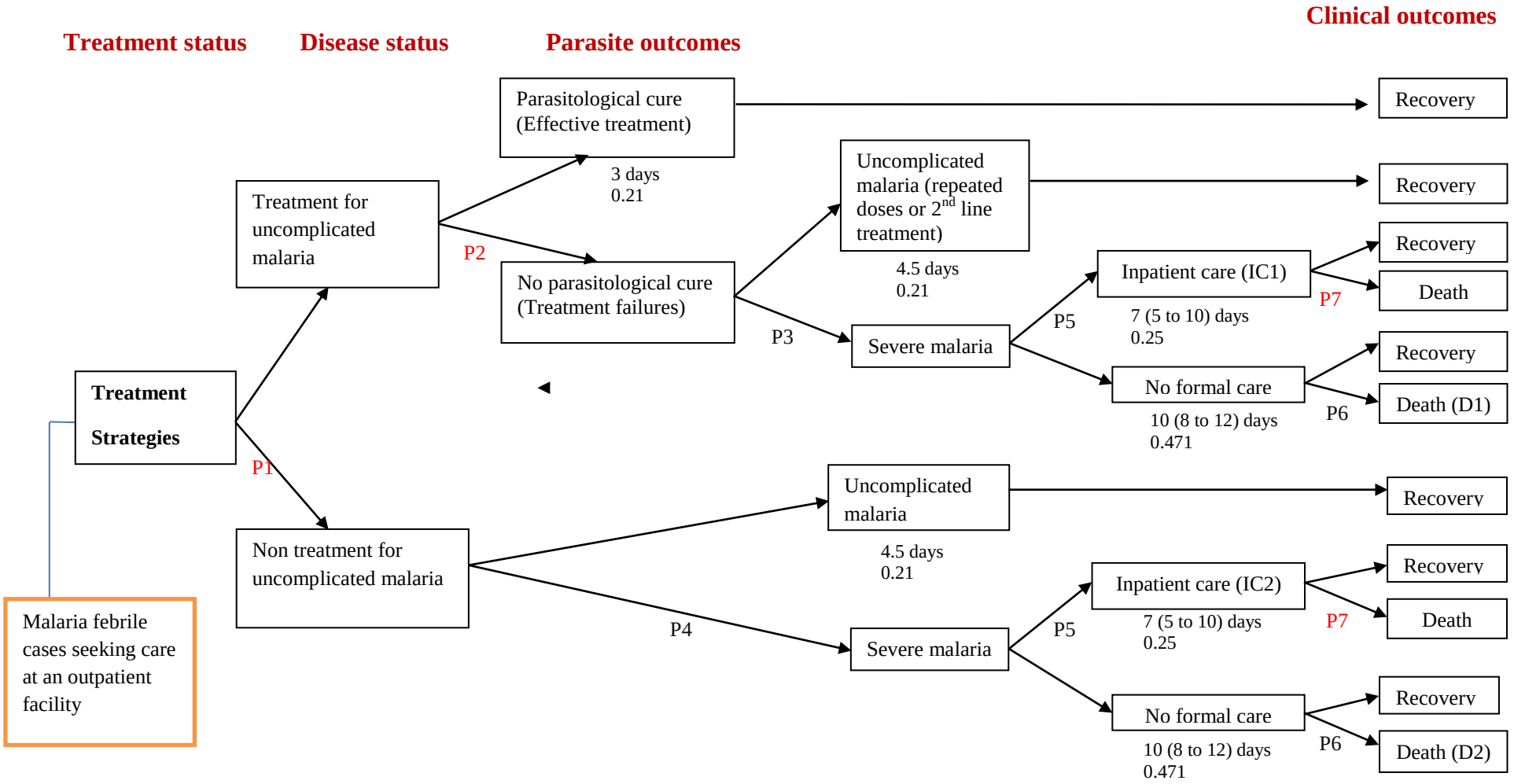


Figure 5-2: Case management decision tree for malaria patients. Transition probabilities are shown below each path and presented in the table 5-2. The duration of the disease and the disability weight are presented below state box. The probabilities in red obtained from OUCRU IBM and in black taken directly from the literature review.

5.2.2 **Data descriptions and adjustments**

5.2.2.1 Estimating the cost between strategies

Types of costs: From the literature review 7 main activities were identified that most countries would have engaged in when they change their national drug policies (Table 5-3).These activities were grouped into 3 different main types of costs that were included in the estimate: the set-up costs, the drug costs, and the case-management costs. The set-up costs were considered as the costs of developing and implementing the new treatment guidelines [224]. The costs associated with the policy change include any increase in the costs of new drugs used, or expenses associated case management. Methods for calculating these costs are described in detail below.

Costing perspectives: In this study, costs were estimated from a societal perspective, which included the costs to the health system and the costs to the patients. This study did not take account of indirect costs (income lost). The set-up costs were mainly incurred by the health system. Drug costs and case-management costs included costs for both the health system and the patients. As the analysis was intended to be incremental, existing infrastructure that would be present without the interventions were not included.

We then used a variety of sources to develop cost estimates for the actual implementation and maintenance of this program. To assure a realistic cost estimate, we attempted to develop a relatively comprehensive list of all potential direct costs including program costs (capital expenditures, primary healthcare worker training, and social marketing programs), drug purchase and distribution costs for switching to single first-line drugs (cycling or sequential) or MFT strategy.

Table 5-3: Costs of changing single first-line drugs

Types of costs		Activities
Set-up costs (Non-recurrent costs)	Costs of developing guideline	Consultation & consensus building & policy formulation
		Revision & production
	Costs of implementation	Training
		Information, education, and communication (IEC)
		Program management and monitoring and evaluation (M/M&E)
Drug costs (Recurrent costs)		Drug procurement and drug distribution (training & monitoring & IEC of the drug delivery)
Case management costs (Recurrent costs)		Case management for uncomplicated and severe cases

Set-up costs: These costs comprised of 5 activities: consultation & consensus building & policy formulation; revision & production of guidelines; training of health workers; information, education and communication (IEC); and program management and monitoring & evaluation (M/M&E). These activities were considered as one-off costs of the campaign, which were expected to last as long as the campaign's useful lifespan. In other words, the costs related these activities are mainly incurred in the first year and are not repeated regularly. The total cost estimates for these 5 activities were obtained from the literature review. Unit costs per person per year were adjusted with the study population in the OUCRU IBM model. A description of activities, unit cost assumptions for each strategy in the first year (2013) are presented in Appendix 14. These projected costs were calculated assuming a year delay for the policy change take

place. All costs were adjusted to 2013 USD using the local consumer price index (CPI) and exchange rates values.

For the sequential/cycling strategy, the costs of consultation (**activity 1)** were considered as fixed costs as these could not vary by scale of implementation (such as population size). These costs were obtained from the cost of changing single first-line drugs from CQ to SP in Tanzania in 2001which were estimated at $63,152 per year for 33 million individuals. The costs of developing & production & printing of IEC materials & drug package envelopes& treatment guidelines **(activity 2)** per capita were estimated at $0.0017 (range: 0.0015 to 0.004). These values were derived from the average costs, min and max costs of the switch from CQ to SP in Tanzania of 3 studies [181,198,205]. These estimates were shown in Chapter 4. The costs of training per capita **(activity 3)** were assumed to cover the training for health personnel in formal health facilities and the training for community health worker. The training per capita costs were estimated at $0.01 ($0.005 to $0.02) [181,198,205]. The training per capita costs of community health workers per capita were estimated at $0.81 (2013 USD) [206] which was assigned for 61% of the study populations that were assumed to reside in rural areas [225]. The costs of IEC (**activity 4**) per person was estimated at $0.007 (0.001 to 0.02).The costs of M/M&E (**activity 5**) were estimated at an average of $0.003 (0.001 to 0.007) per person at risk per year.

The set-up costs of cycling and sequential strategy were the sum of the discounted set-up costs incurred at each future time the policy changes. These future set-up costs were discounted to 2013 USD based on average annual discount rate of 3%.

The set-up costs of a MFT strategy were expected to be higher than the set-up costs of cycling/sequential strategy because they were the more complex strategies and therefore require additional activities. These extra activities would lead to extra cost as compared with the introduction of a single first-line drug. The MFT strategy required strengthening the implementation team therefore the cost of policy formulation (**activity 1**) was assumed to increase to $289,163 per year for 33 million individuals. This value was derived from the strengthening the implementation team [197].The MFT strategy was assumed to incur higher costs of revision and production treatment guidelines (**activity 2)** as more production of guidance documents for local district managers. This cost was assumed to be $0.002 per person which was derived from the assumption that more guidelines were produced at districts [198]. The MFT strategy required enhanced training **(activity 3).** The training costs per capita per year of health personnel were increased to $0.11 (0.008 to 0.05) which was derived from the average costs of the switch from SP to ACT of 7 scenarios in a Tanzania study [197]. The costs of training health village workers per person per year was equal to $1.27 (2013 USD) [206]. The MFT strategy required more communication and publicity costs (IEC) (activity 4).Higher costs of monitoring per capita per year (activity 5) were assumed for the MFT strategy; which were $0.02 (range: 0.01 to 0.05) collected from policy change of SP to ACT for 7 scenarios in Tanzania [197].

The drug costs (the cost of producing and delivering the ACT drug):

Implementing the MFT strategy implied an increase in the cost of drugs, so these are kept separate from the cost of case-management. The drug costs comprised 2 components, the costs of drug purchase and the costs of delivering the drugs from the

central level to the health facilities within a country. A unit of ACT was defined as one treatment course packaged in a single unit pack. The age-specific drug cost per treatment course were then multiplied by the number of malaria cases generated from the OUCRU IBM model to obtain the annual drug costs per strategy.

The drug cost of ACTs were obtained from the "Global Fund price and quality" report of 2013. This was the Global Fund's reference price negotiated with manufacturer of ACTs for 4 different age-groups in malaria endemic countries. This study considered the three most widely used ACTs which are Artemether-lumefantrine (AL), Dihydroartemisinin-piperaquine (DHA-PPQ), Artesunate-amodiaquine (ASAQ). This analysis derived the median drug price per tablet for each drug (Appendix 15). The cost per tablet was adjusted for the dosage treatment to reflect the manufacturing drug price per one full treatment course (3-day oral regimens). Vietnamese malaria treatment guidelines 2013 (DHA-PPQ) & Tanzania treatment guidelines 2005 (AL) and WHO guidelines 2010 (AS-AQ) for 4 age-groups were calculated (Appendix 15). The unit drug prices for MFT strategy were assumed to be higher than the sequential/cycling strategy based on the premise that a volume discount was reduced or lost when the variety of drug assortment increased [179]. A volume discount of 1% for 100,000 tablets was assumed.

The cost of delivering drugs in the sequential and cycling strategies was similar since both strategies were delivered using existing health system infrastructure to deliver the drugs to the local health centers. The costs of delivering ACT from the central-level to health facilities were obtained from [218] which was equal to $0.2 normalised to 1

USD of unit drug price. This means that for every $1 unit cost of the drug, $0.2 was added for local delivery including storage and distribution.

The cost of delivering drugs in the MFT strategy was assumed to be higher than the sequential strategy due to more complex distribution strategies. This strategy required greater resource requirements associated with creating a new drug delivery system for a new target population that has been previously served by the existing routine drug program. Specifically, higher cost of delivering drugs come from 2 aspects consisting of safety holding costs, and the costs of monitoring drugs. The assumption of higher safety holding costs were based on the study [179]. In this study, the costs of drug delivery were assumed to be 100% higher for the MFT strategy than the sequential strategy. Appendix 14 reports the unit drug price by age and by strategy after adjusting volume discount for the manufacturing drug prices.

The case management costs: The case management costs combined the costs of uncomplicated cases and severe cases, but excluded the first-line drug cost for uncomplicated malaria that differs by strategy (as described above). The costs per uncomplicated case were defined as the direct costs of an uncomplicated malaria case seeking care at formal-sector facilities (Appendix 14). The cost of treating an uncomplicated case were assumed to be $5.84 (range 2.36-23.65) as in [226]. This cost covered the cost of consultation at formal-facilities (such as health centers, dispensaries, hospitals) and diagnosis (either the cost of RDT or microscopy), and the patient costs per outpatient visit when visiting formal sector outpatient facilities (excluding fees) such as travel expenses, expenses related to medical supplies, and

non-medical supplies for example the purchases of food and drinks or costs of spending the night away from home while seeking care. The healthcare costs per severe case in adult and children were $64.50 (range 26.99-288.79)[226] that included the inpatient costs and the cost of 7 days of intravenous *artesunate* used as first-line treatment of severe malaria, and the cost of treating specific complications. As for the treatment failures for uncomplicated cases, the costs of repeated cases were assumed to include the repeated first-line ACT drug plus the cost of consultation and diagnosis of uncomplicated case. The cost of the second-line drug (quinine)was estimated at $21[174]. These unit costs of case management were similar for different strategies across all the health system scenarios.

5.2.2.2 Estimating the DALYs associated with the strategies

The primary measure of health outcome used was the disability adjusted life year (DALY). DALYs accounted for both years of life lost (YLLs) due to early mortality and years of life lived with disability (YLD), calculated using standard methods [19]. The YLLs were calculated assuming age-specific life expectancies based on the life-tables from two countries: Tanzania (high transmission areas) and Vietnam (low transmission areas). YLD were calculated on the basis of the duration of disability and respective disability weights for uncomplicated and severe malaria. Disability weights of 0.024and 0.21 for mild and severe acute episodes of infectious diseases obtained from the Global burden of Disease study were applied for mild and severe malaria (Table 5.4). In this study YLLs, YLDs were presented without discounting and age-weight as per most recent guidelines [227]but DALYs occurring in the future were discounted using an annual rate of 3%). The YLLs and YLDs were calculated for each

of episode (uncomplicated or severe) accruing over a 20 year time horizon for different treatment strategies. The DALYs were the sum of YLLs and YLDs for all age-groups.

Equation 7: Calculation of DALYs without discounting and age weighting:

The DALY is calculated as: DALY = YLL + YLD

where: YLL = years of life lost due to premature mortality. YLD = years lived with disability.

The YLL metric essentially corresponded to the number of deaths multiplied by the standard life expectancy at the age at which death occurs. YLLs were calculated assuming age-specific life expectancies from Vietnamese and Tanzania life-tables. Calculating the YLL for a given cause, age or sex, is:

YLL = N x L

Where: N = number of deaths. L = standard life expectancy at age of death (in years).

The basic formula of YLD (without applying social preferences) for one disabling event is:

YLD = I x DW x L

Where: YLD = years lived with disability. I = number of incident cases. DW = disability weight. L = average duration of disability (years)

Table 5-4: Parameter values for effectiveness (DALYs)

Description of parameter	Central value	Lower value	Upper value	Distribution	Reference
Average duration of illness when uncomplicated patients are successfully treated (days)	3 days	2	5	Triangle (mode =3, min-max:2-5)	Maire et al (2011) [223]
Duration of illness for uncomplicated patients who are	4.5 days	3	7	Triangle (mode =4.5, min-max:3-7)	Maire et al (2011) [223]

Description of parameter	Central value	Lower value	Upper value	Distribution	Reference
unsuccessfully treated and untreated (days)					
Duration of untreated uncomplicated malaria	7 days	5	10	Triangle (mode =7, min-max 5-10)	Goodman et al (2001) [182]
Average length of stay for inpatient treated severe patients (days) who then recovers or die	7 days	5	10	Triangle (mode =7, min-max:5-10)	Maire et al (2011) [223]
Average length of stay when patient dies (days)	2 days	1.6	2.4	Triangle (mode =2, min-max:1.6-2.4)	Maire et al (2011) [223]
Duration of severe malaria without inpatient care, and recovers and die	10 days	8	12		Assumption
Disability weight for uncomplicated malaria for successfully and unsuccessfully treated/ untreated	0.21			Fixed value	Murray et al (2012) [19]
Disability weight for severe malaria, inpatientwho then recovers or die	0.25			Fixed value	Murray et al (2012) [19]
Disability weight for untreated severe malaria recovers and die	0.473			Fixed value	Tediosi et al (2006) [195]

5.2.3 **Analysis of simulated outputs**

5.2.3.1 Statistical differences in costs and DALYs

The median and mean for each category of cost and for total costs in each strategy was calculated. The non-parametric bootstrap method was employed to examine the differences of accumulated discounted costs over 20 years between MFT versus sequential strategy, MFT versus cycling strategy, and cycling versus sequential strategy. The 95% confidence intervals around the cost differences were then calculated in order to determine whether these differences were likely due to chance. The 95% bootstrapped confidence intervals for the mean differences were measured based on the percentile bootstrap method. Non-parametric bootstrap methods were employed to examine differences in YLLs, YLDs, and DALYs as well.

5.2.3.2 Incremental cost-effectiveness

Incremental cost-effectiveness ratios (ICERs) were calculated as the differences in median total costs divided by the difference in median DALYs between strategies, where one strategy was more costly and more effective than an alternative. The ICER expresses the additional cost required in order to avert a DALY. In scenarios where one intervention was more effective but costlier than its comparators, the lower the ICER become, the more attractive was the new intervention. Three types of ICERs were considered as following:

ICER MFT compared with Sequential strategy= (cost MFT – cost Sequential strategy) / (DALYs averted by MFT – DALYs averted by Sequential strategy)

ICER MFT compared with Cycling strategy= (cost MFT – cost Cycling strategy) / (DALYs averted by MFT – DALYs averted by Cycling strategy)

ICER Cycling compared with Sequential strategy= (cost Cycling – cost Sequential strategy) / (DALYs averted by Cycling– DALYs averted by Sequential strategy)

In this study, the WTP threshold for the high transmission settings was assumed to be the median GNI per capita of Sub- Saharan Africa, $1,055. The WTP threshold for the low transmission settings was assumed to be the median GNI per capita of South East Asian countries $4,125.

5.2.3.3 Sensitivity analysis

Sensitivity analyses were conducted for both epidemiological parameters and percentage change cost between sequential strategy and MFT strategies, as these estimates were not based on high-level evidence.

Sensitivity analysis of epidemiological input values, treatment coverage, cost and DALY values.

The sensitivity analyses were first focus on key parameters in the OUCRU IBM model. These were the treatment coverage (0.5, 0.6, 0.7, 0.8, and 0.9), and different biological fitness cost for drug-resistant genotypes (0.001, 0.005 0.01) in low/high transmission settings (annual EIR of 1.33 and 20.3 infectious bites per person per year). In the absence of the drug, a parasite with the resistant mutation did not have a survival advantage and therefore did not live long or reproduced faster than the non-mutants and this survival disadvantage was known as fitness cost of resistance (CR) to having the mutation [180]. The OUCRU IBM model produced simulated outputs for all configurations of treatment coverage, fitness cost and for low and high transmission settings resulting in30 scenarios.

For each of the 30 scenarios, the ICERs, the NMB, the acceptability curves between strategies were calculated. The sensitivity analyses then investigated the effect that varying health economic parameters individually would have on the cost per DALY averted (the ICERs) or the NMBs between strategies. This required varying transition probabilities, health seeking treatment and DALY values by their low and high estimates. The cost parameters were varied by +/-50% percentage, as commonly practiced in costing studies [223]. Each simulated scenario was run separately for low and high transmission settings with each of 1,000 bootstrap replicates of cost and DALYs differences between strategies. For each parameter, the contribution to uncertainty of the NMB was measured by differences between the median NMBs in the baseline scenarios and the resampled scenarios. These differences were plotted in rank order to indicate which parameter contributes the most uncertainty to the median NMB. This one-way sensitivity analysis is displayed using a Tornado graph for the 30 different scenarios. The epidemiological parameters are listed as in Table 5.5:

Table 5-5: Sensitivity analysis on epidemiological parameters for low and high transmission settings

Beta	**Cost of resistance (CR)**	**Treatment coverage (f)**
0.08	0.01	0.5
	0.005	0.6
	0.001	0.7
		0.8
		0.9

Probabilistic sensitivity analysis (PSA):

Standard beta distributions, bounded by 0 and 1, were assigned for parameters representing probabilities. Log normal and gamma distributions bounded by 0 with a

positive skewed used for cost parameters. Point estimates (fixed values) were used for parameters, which were known with absolute certainty. For each combination of treatment coverage and fitness cost of resistance in low and high transmission settings, the model was iterated 1,000 times. At each iteration, input parameter values were chosen at random from the defined probability distributions. The calculated ICERs were calculated and compared with the WTPs threshold to determine whether the strategy would be considered cost-effective in low and middle-income countries. The PSA approach was applied to both the epidemiological and case management parameters but not simultaneously. First, the values of the parameters in the OUCRU IBM model were randomly drawn from defined distributions. Then the output of the OUCRU IBM model became the inputs of the economic decision model.

I used these outputs from OUCRU IBM along with the cost parameters, DALY weights and other epidemiological parameters such as transition probabilities and the duration of disability as the inputs for my economic decision model, I ran economic decision case management model to calculate costs and DALYs for each age-group (from 0-1 to 79- 80) for each year (during 20 years) for each simulated scenario. The values of the cost parameters, DALY weights, the other epidemiological parameters such as transition probabilities and the duration of disability were all randomly drawn from triangle or beta distributions.

Cost-effectiveness acceptability curves (CEAC):

The CEACs illustrated the probabilities that the new intervention (MFT strategy for example) would be cost-effective in comparison to either the cycling or sequential strategy.

Threshold analysis on key cost assumptions:

This sensitivity analysis focused on the key costs drivers. For each of the 30 scenarios, I assumed that the costs of MFT strategy was getting more expensive in key activities such as M/M&E costs, training costs, and drug costs. These costs increased by a 10% increment to identify the cost thresholds at which MFT was no longer cost-effective. Two relevant cost-thresholds were identified: i) the point at which MFT became more costly than either of the two comparator strategies; or ii) the point at which the MFT strategy was no longer cost-effective, as defined by a probability of less than 50% of being cost-effective in comparison with either the sequential strategy or the cycling strategy, at a WTP threshold of US$1,055 per DALY averted and $4,125in high transmission settings and low transmission settings respectively. This threshold analysis were applied to all the epidemiological scenarios above.

Expected value of information analysis (EVPI):

In health economics, it is supposed that there is always some degree of uncertainty surrounding the decision of adopting a new treatment technology, because there was always a chance that the decision turned out to be wrong. The expected value of perfect information analysis tried to measure the expected cost of the wrong strategy being adopted (i.e. the probability of this occurring and the cost, including both adverse health outcomes). Further research could reduce this uncertainty or even avoid it altogether. The expected value of perfect information (EVPI) is an expression of the value of such research, since perfect information could eliminate the possibility of making the wrong decision, at least from a theoretical perspective. To quantify the value of acquiring additional information on the health economic parameters, this

study computed the theoretical EVPI based on the net-benefit approaches [228]. The mathematical algorithm was described in[155]&[228].

5.3 **Results**

This section presents the total cost for each strategy and differences in total costs between strategies with 95% bootstrapped confidence intervals, followed by the DALYs for each strategy, and the cost-effectiveness results.

5.3.1 **Results of costs**

5.3.1.1 The total cost for strategies in a low and high transmission setting

Figure 5-3 present the discounted total cost for a population of 1 million people across different strategies (MFT strategy, cycling and sequential strategy) over 20 years in low and high transmission settings (EIR=1.3 and 20.3 infectious bites per year respectively). The total costs covered the set-up costs, the drug costs, and the cost of case management for treating uncomplicated and severe episodes. The MFT strategy was associated with the lowest cost among the 3 strategies across all 15 scenarios in both low and high transmission settings.

For the low transmission settings, the implementation of the MFT strategy was associated with an average cost ranging from the lowest value of $399,105 (at 90% treatment coverage and 1% fitness cost) to the highest value of $2.7 million (at 50% treatment coverage and 0.1% fitness cost) (Appendix 16). The MFT strategy was the cheapest strategy compared to the single first-line strategies across a 15 combinations of the fitness cost levels and values of treatment coverage. This is because the MFT

strategy delayed the emergence and spread of ACT drug resistance, leading to reduced morbidity and mortality, and in turn lowered the cost of case management and set-up costs. Since the cost of case management was the main driver of the total costs of 3 strategies (60% to 67%), followed by the set-up costs (20% to 30%) and the drug costs (5%). The MFT strategy was associated with the lowest cost of management leading to the lowest total cost among these 3 strategies.

In low transmission settings, increasing treatment coverage reduced the total cost of implementation for 3 strategies over 20 years regardless of fitness cost values. The reason was that higher treatment coverages prevented more malaria cases and lowered the malaria prevalence over the long term and overall onward malaria transmission. The cost-saving from reduced future treatment was greater than the set-up costs in the beginning which is the result of higher treatment coverage. As a result, the total costs for 3 strategies over 20 years were lower as the treatment coverage increased. This finding highlighted the fact if policy makers in low transmission settings devote resources to expanding treatment coverage in the beginning and they will save money over the long-term from reduced treatment in the future. This refutes the argument that increasing treatment coverage would involve higher likelihood of developing resistance to the drug and higher treatment failures which might cause greater financial burden for the health system over the long term. Increasing treatment coverage reduced total costs of infection and treatment over 20 years for either strategies had also been demonstrated in [229]. However, this study did not differentiate the findings according to transmission intensity.

Additionally, the variation in the total costs was particularly large once the treatment coverage reached 90%. In the low transmission settings, for treatment coverage≥0·7, there were more than 50% of 100 simulations that achieved extinction or near extinction in which the number of treatment failures (NTFs) were less than 0·5 per 100 persons per year discounted at 3% annually. As a result, the numbers of cases were scattered widely leading to the accumulative discounted total costs over 20 years vary widely in these situations.

For the high transmission settings, the cost of a MFT strategy varied from $3.8 million (at 90% treatment coverage and 1% fitness cost) to $4.9 million (at 50% treatment coverage and 0.1% fitness cost). The MFT strategy remained the cheapest strategy across 30 different scenarios with different combination of treatment coverage, fitness costs and transmission intensity. Potential advantages of MFT strategy over cycling or sequential strategy included the reductions in overall treatment failures rates observed in the OUCRU IBM model, cases and death, and (even taking account of re-infection rates might not change the results).

The pattern of increasing treatment coverage reducing the total costs for three strategies were not as pronounced in the high transmission setting. Higher treatment coverage still reduced malaria cases in the future but the cost-saving from reduced future treatment was countered by the incremental cost of management of higher treatment coverage.

The variations around the median costs were narrower in the high transmission settings because extinction did not occur here. The advantage of the MFT strategy over the

single first-line drugs in term of costs were seen clearly in the high transmission settings.

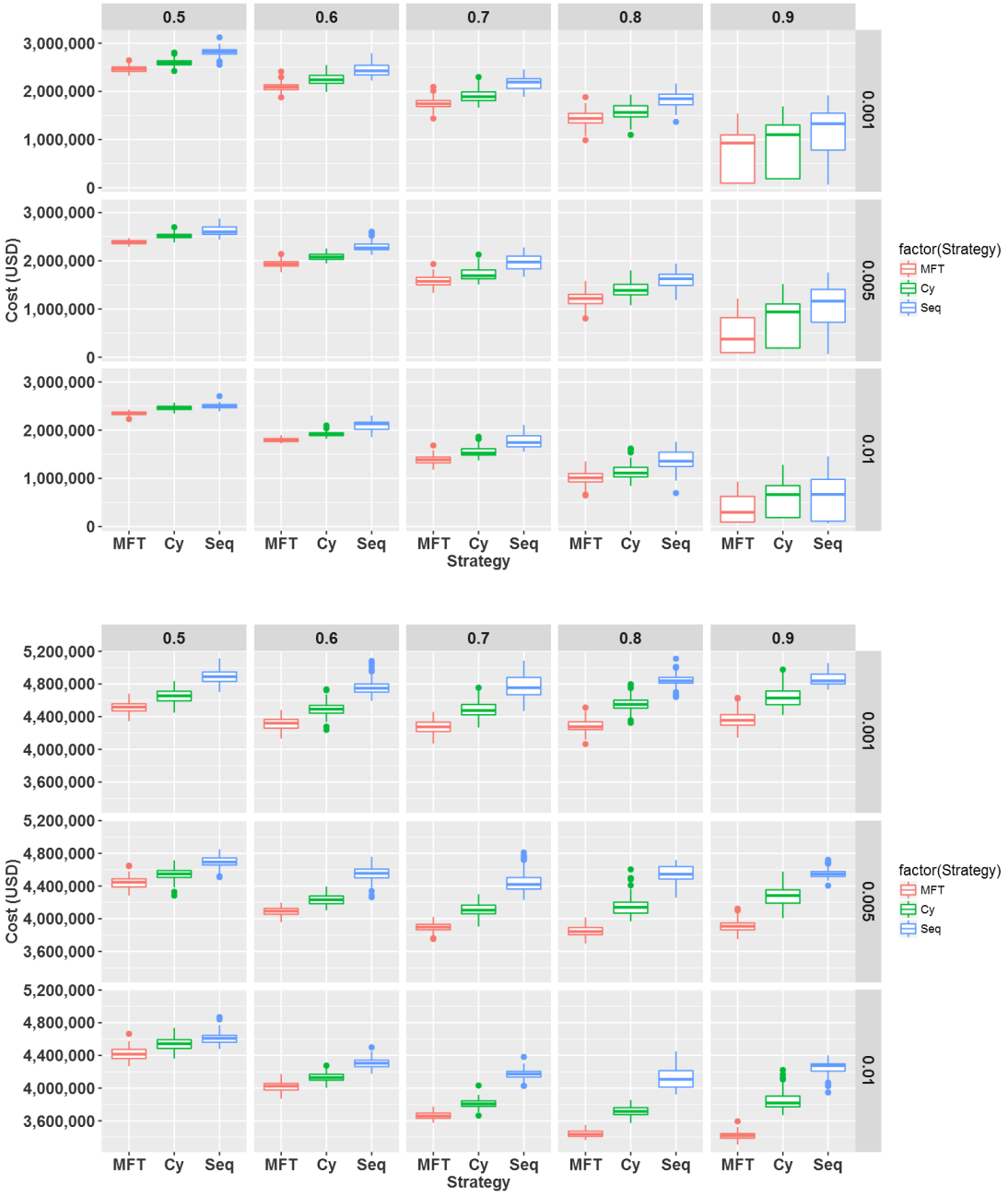


Figure 5-3: The mean discounted total cost for different strategies, different costs of resistance (C_R), and different treatment coverages (f) in a low-transmission setting with an entomological inoculation rate of 1.3 for the first graph, and a high transmission setting with an entomological inoculation rate of 20.3 for the second

graph. The costs are in 2013 US dollars. The y-axis represents the costs in US dollars and the x-axis shows the strategies which are MFT, cycling (Cy) and Sequential strategy (Seq). Each column shows the mean total costs results of 100 model simulations with bars spanning the IQR. The total costs are lower for multiple first-line therapies than for cycling or sequential strategies across different scenarios. For *treatment coverage* ≥0·8 in the low transmission settings, the costs exhibit wide distribution. The costs exhibit narrow distribution across for other scenarios.

5.3.1.2 Differences in total costs with 95% confidence intervals

The MFT strategy was significantly cheaper than both of the single first-line strategies at 95% confidence intervals according to the bootstrapping method. The MFT strategy was preferred at all levels of coverage, and fitness costs of resistance and for both low and high transmission settings over 20-year period of policy-making. The differences in costs between the MFT strategies versus sequential strategies were greater than those between the MFT strategies and the cycling strategies. These savings emanated the fact that MFT strategy was associated with fewer patients and failed treatment leading to lower incidence of both uncomplicated and severe malaria cases (the MFT strategy had an average of 10% fewer cases than the sequential strategy according to the OUCRU IBM model).

For example, when compared to sequential strategy, the MFT strategy averted total costs per one million individuals on an average between $159,618 (95% CI -179,054 to -141,366) [5% reduction] at 50% coverage and 1% fitness costs and -$403,946 (95%CI -$661,682 to -$55,743) [65% reduction] at 90% treatment coverage and 0.5% fitness in a low transmission setting. A negative value implied that the MFT strategy less costly than single first-line strategies. As for the high transmission settings, the. differences in costs between the MFT strategy and sequential strategy were between -$

216,254(95% CI -$246,565 to -$190,674) [4% reduction] at 50% coverage and 1% fitness cost to $949,581 (95%CI -$966,125 to -$933,671) [18% reduction] at 90% treatment coverage and 1% fitness costs (Appendix 16).

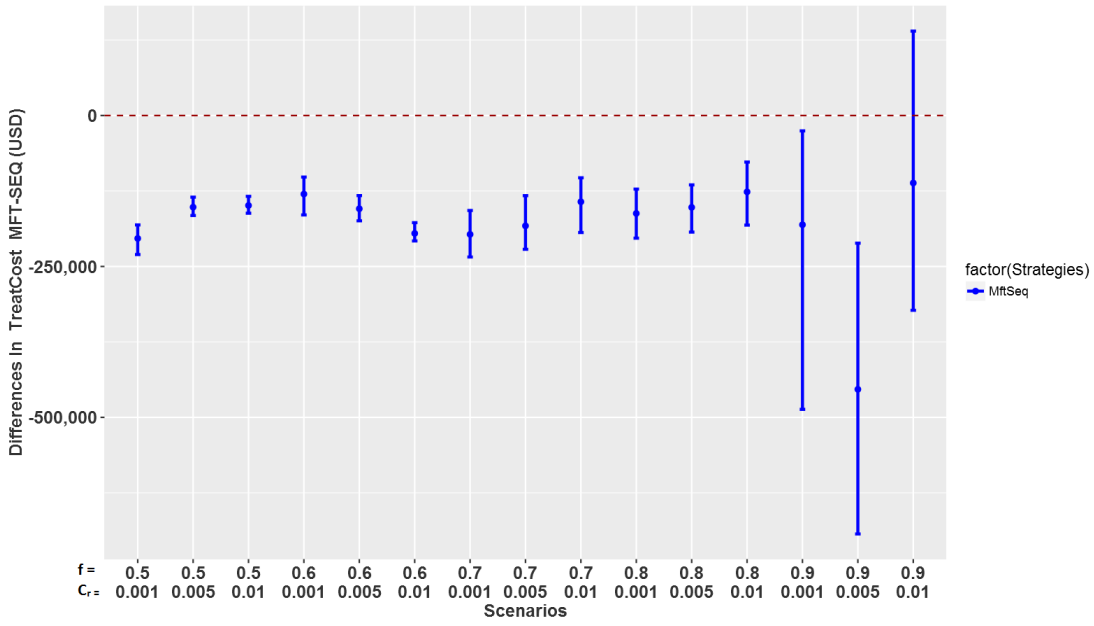
5.3.1.4 The differences in set-up costs, case management costs, and drug costs with 95% confidence intervals

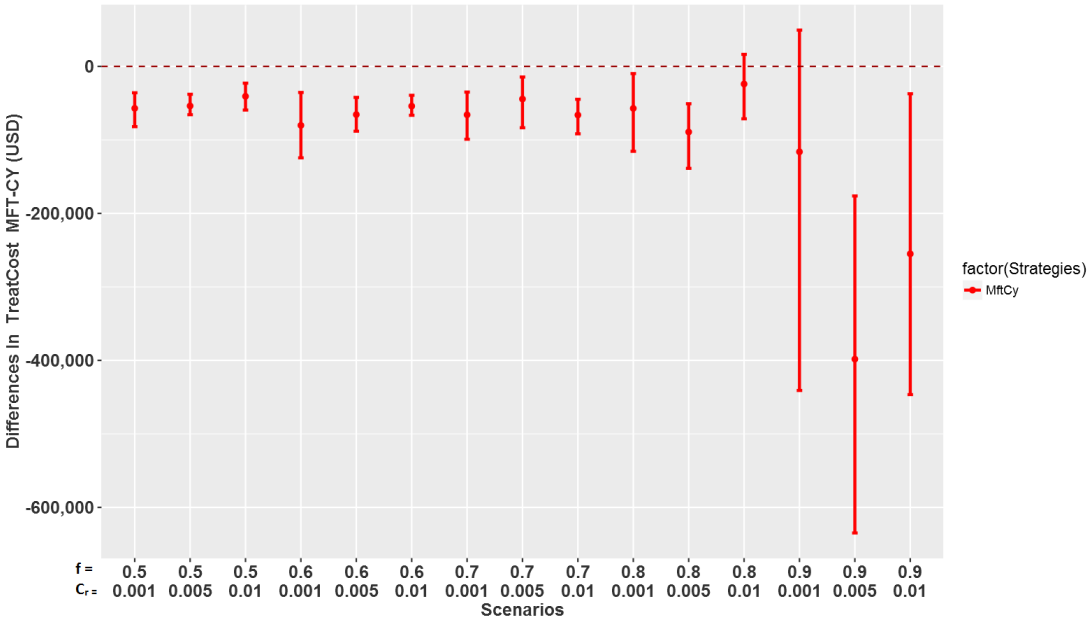
The first and second graphs in Figure 5-4 presents the median differences in case-management costs between two pairs of strategies: MFT – Sequential (the first graph), MFT – cycling (the second graph) for 15 different scenarios corresponding to treatment coverage (50% - 90%) and fitness cost of resistance (0.1, 0.005, and 0.001) in a low transmission setting with an entomological inoculation rate of 1·3

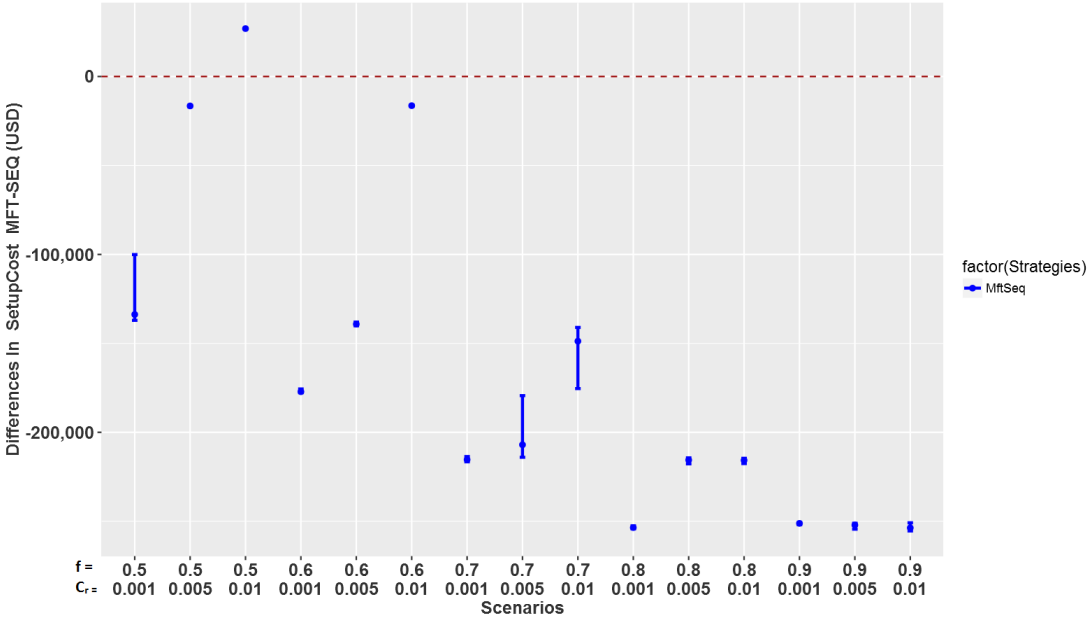
The cost of case management associated with the MFT strategy from the provider's perspective was significantly lower than the sequential strategy for 14 out of 15 scenarios at low transmission intensity. However, the MFT strategy was not significantly different from the sequential strategy for a scenario with highest treatment coverage (90%) and highest fitness cost of resistance (1%) (mean difference in costs -$103,255(95% CI -$316,597 to $137, 157 based on bootstrap test). Although the MFT strategy averted more malaria episodes (2% and 5%), treatment failures (12% and 46%) and death (3% and 6%) than the sequential strategy in low and high transmission settings, the differences in malaria cases between these two strategies were not significantly large because more simulation runs achieved the extinction, leading to the non-significant differences in total costs. These two strategies however

could be interpreted as comparable in terms of costs because elimination was seen more often with MFT strategies.

The cost of case management associated with the MFT strategy were significantly lower than cycling strategy for 13 out of 15 scenarios in areas with low transmission. The non-significant differences seen in 2 scenarios were when treatment coverage reached to either 80% or 90% and the fitness cost of values varied around 0.1% and 1%. The non-significant differences in costs were also attributable to more simulation achieving extinction in the low transmission settings.




Differences In TreatCost MFT-CY (USD)
0
-200,000
-400,000
-600,000
f = 0.5 0.5 0.5 0.6 0.6 0.6 0.7 0.7 0.7 0.8 0.8 0.8 0.9 0.9 0.9
Cr = 0.001 0.005 0.01 0.001 0.005 0.01 0.001 0.005 0.01 0.001 0.005 0.01 0.001 0.005 0.01
Scenarios
factor(Strategies)
MftCy


Differences In SetupCost MFT-SEQ (USD)
0
-100,000
-200,000
f = 0.5 0.5 0.5 0.6 0.6 0.6 0.7 0.7 0.7 0.8 0.8 0.8 0.9 0.9 0.9
Cr = 0.001 0.005 0.01 0.001 0.005 0.01 0.001 0.005 0.01 0.001 0.005 0.01 0.001 0.005 0.01
Scenarios
factor(Strategies)
MftSeq

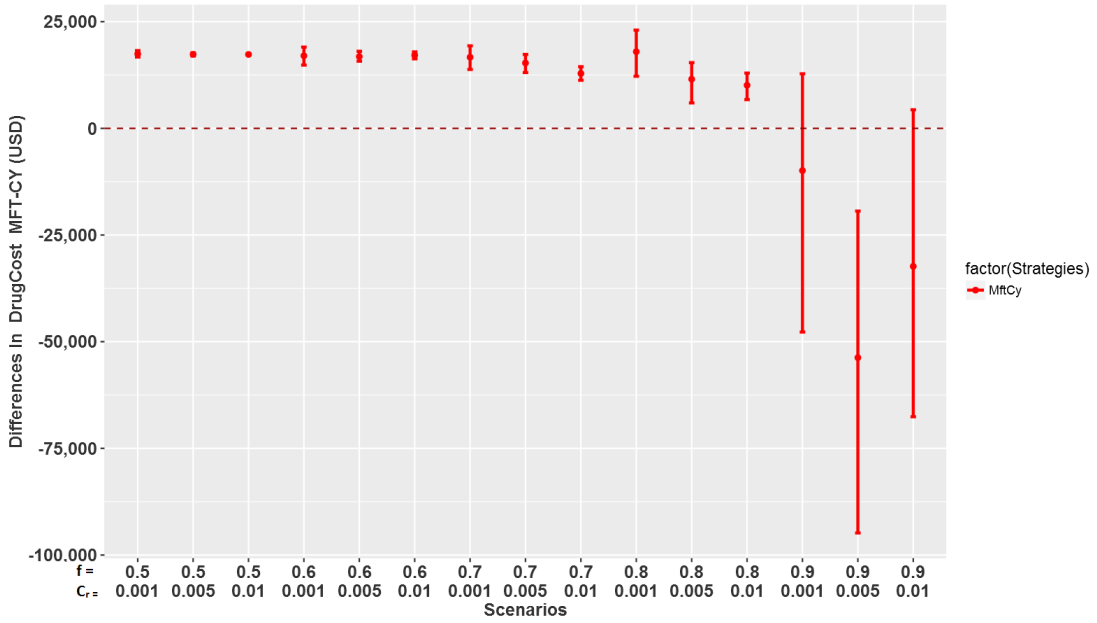


Figure 5-4: Mean differences **in case management costs** with 95% confidence intervals for the MFT strategy and sequential strategy (the first graph) and between the MFT strategy and the cycling strategy (the second graph) across different costs of resistance (CR), and different treatment coverages (f) over 20 years in a low transmission setting with an entomological inoculation rate of 1·3. The third graph represents the mean differences in **set-up costs** with 95% confidence intervals in the high transmission settings with EIR of 20.3. The fourth graph depicts the mean differences in **drug costs** with 95% confidence intervals in the low transmission settings with EIR of 1.3. The costs are in 2013 US dollars. The y-axis represents the cost in US dollars. The x-axis represents the 15 different scenarios corresponding to different treatment coverage levels (f) (50% to 60% to 70% to 80% to 90%), and different biological fitness costs for drug-resistant genotypes (CR) (0.1% 0.5% 1%) from left to right in the graph. For example, "7005" is treatment coverage 70% and fitness cost of resistance of 0.05%. These results were based on the 1000 bootstrapped and probabilistic simulations of differences in costs between strategies being compared The dot represents the mean difference in total costs per 1 million population during the 20-year simulation spanning with 95% credible range, discounted at 3%. The colours of the dots represent the pair of strategies being compared which are MFT strategy versus the sequential strategy (blue), strategy versus the cycling strategy (red). The red dash line indicates the mean differences in costs between strategies were negligible. The dots and the 95% credible range lie below the red dash line indicate the MFT strategy was associated with significantly cheaper costs and vice versa.

The MFT strategy was associated with significantly cheaper set-up costs than the cycling strategy for 30/30 combination values of treatment coverage, fitness costs, and transmission settings, and 29 out of 30 combinations of these parameter values when compared to the sequential strategy. The set-up costs represented a minimum initial investment needed at national level to implement the treatment guideline. The set-up costs included the costs of consensus meeting (10%), the revision of the guidelines (10%), the training of health workers (40%), the M&E (20%), the IEC (20%). The set-up costs of the MFT strategy were cheaper because it incurred fewer policy changes. In fact this strategy experienced only one policy change during 20 years which was the change incurred at the start of the implementation. On the other hand, the cycling or sequential strategy incurred an average of 5 policy changes during the 20 year period because that these strategies experienced higher frequency of drug resistance which inclined them to reach to the 10% treatment failure threshold more frequently. There were some situations in which the sequential first-line drugs resulted in more than one policy changes within a short period of time. This reflects the fact that the efficacy of this strategy faded off rapidly after the resistance first emerged.

Nevertheless the set-up cost of the MFT strategy was significantly more expensive ($26,611 95% CI $26,347 to $26,867) than the sequential strategy (Figure 5-4 third graph) in one scenario of the high transmission setting when the treatment coverage reached to 50% and fitness cost were leveled off at 1% because the sequential strategy reached to the 10% threshold of the treatment failures once during 20 years; therefore this strategy experienced only one policy change during its implementation years. As a result, the total set-up costs of one policy change for the MFT strategy were likely to

be two times higher than the set-up costs of one policy change for the sequential strategy. The interpretation of this is that when the fitness cost of resistance was as least 1% and the treatment coverage was at its lowest value of 50%, the drugs were less frequently used in the population; low drug pressure tended to delay the growth of resistant parasites. The resistant parasite with high mutation could not survive well in the normal environment without the presence of drugs. Consequently, the evolution of drug resistance did not happen frequently for the sequential strategy. This was also true for all the strategies. In addition many people were likely to develop immunity in the high transmission, so they may not show clinical symptoms that needed treatment. Therefore, in this scenario, the sequential strategy was less likely to meet the 10% treatment failure threshold for a short or long period of time. In this circumstance, the MFT strategy also experienced low treatment failures, and despite the high initial set-up costs, this strategy maintained its benefits by averting 12.5% more treatment failures than the sequential strategy.

On the other hand, the drug costs of the MFT strategy were significantly costlier than both of the single first-line drug strategies in all the scenarios of different treatment coverage, fitness cost values in areas of the high transmission. The MFT strategy incurred higher total drug costs per 1 million population because the drug prices per treatment course of this strategy were 30% higher than the single first-line strategies, while the MFT strategy averted an average of 10% more malaria episodes compared to the single first-line strategy. Therefore the high drug price of the MFT strategy could not be offset by the reduction in the number of malaria cases.

In summary, adopting the MFT strategy for malaria treatment requires additional financing for setting up at the beginning and higher costs of drug purchases, but reduces the overall cost of malaria treatment in the long-term.

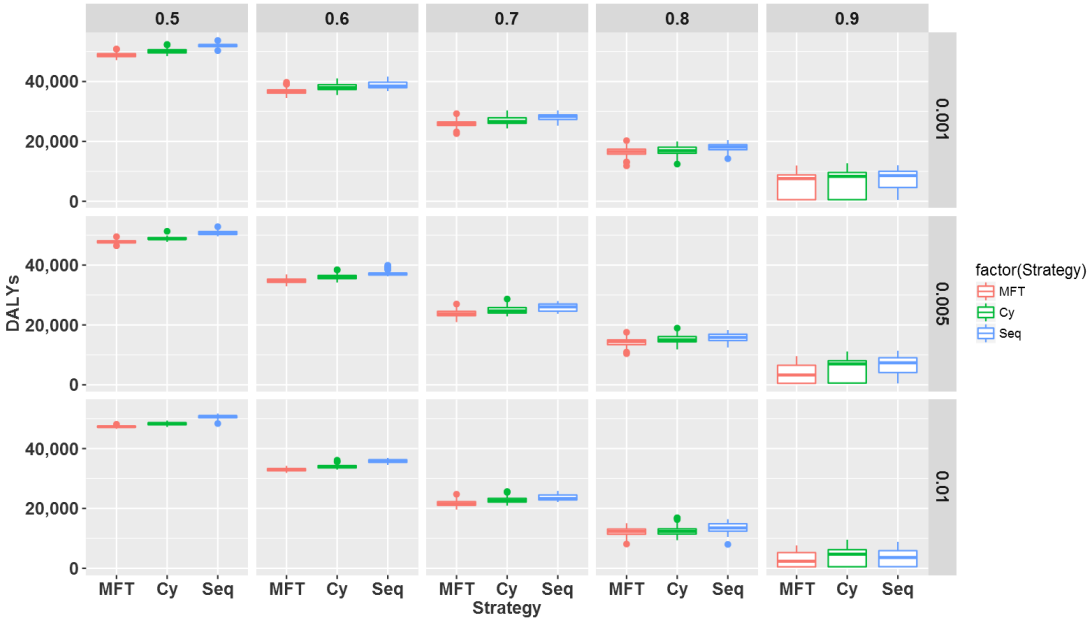
5.3.2 **Impact on health outcomes (DALYs)**

5.3.2.1 The DALYs for strategies in a low and high transmission setting

Figure 5-5 presents the estimates the malaria burden in terms of discounted DALYs for 1 million people over 20 years in areas of low and high transmission. The DALYs were determined by the incidence of uncomplicated cases, severe cases, and deaths.

For the low transmission settings, the probabilistic simulations suggested that the MFT strategy resulted in the largest reduction of DALYs across different coverage levels of treatment, and fitness cost of resistance values in both low/high transmission settings. The MFT strategy was associated with an average DALYs 46,742 DALYs and 2,326 DALYs per 1 million population as treatment coverage scaled up from 50% to 90% and the fitness cost of resistance increased from 0.1% to 1% (Appendix 17). In the low transmission, we see the pattern as in the results of costs that increasing treatment coverage reduced the DALYs for three strategies over 20 years regardless of fitness cost values. Higher treatment coverage prevented more malaria cases and mortality and therefore reduced overall onward malaria transmission. Additionally, the variation in the DALYs was particularly large once the treatment coverage reached 90%, with high proportion of simulations achieving extinction or near-extinction. The cumulative DALYs over 20 years varied widely in these situations.

For the high transmission settings, the MFT strategy was associated with between 199,320 DALYs and 59,215DALYs per 1 million population as treatment coverage scaled up from 50% to 90% and the fitness cost of resistance increased from 0.1% to 1%. Higher treatment coverage and the fitness cost of resistance reduced DALYs for all strategies. Across 15 scenarios the YLLs accounted for over 90% of the DALYs. Since most of the DALYs were due to mortality, the differences in mortality between strategies determined the differences in DALYs. The YLDs represented a small fraction of the total burden of diseases because duration of malaria illness only7 to 10 days if the person recovers. The MFT strategy was associated with the lowest DALYs among these 3 strategies indicating that the MFT strategy averted most death and malaria cases than the single first-line strategies.



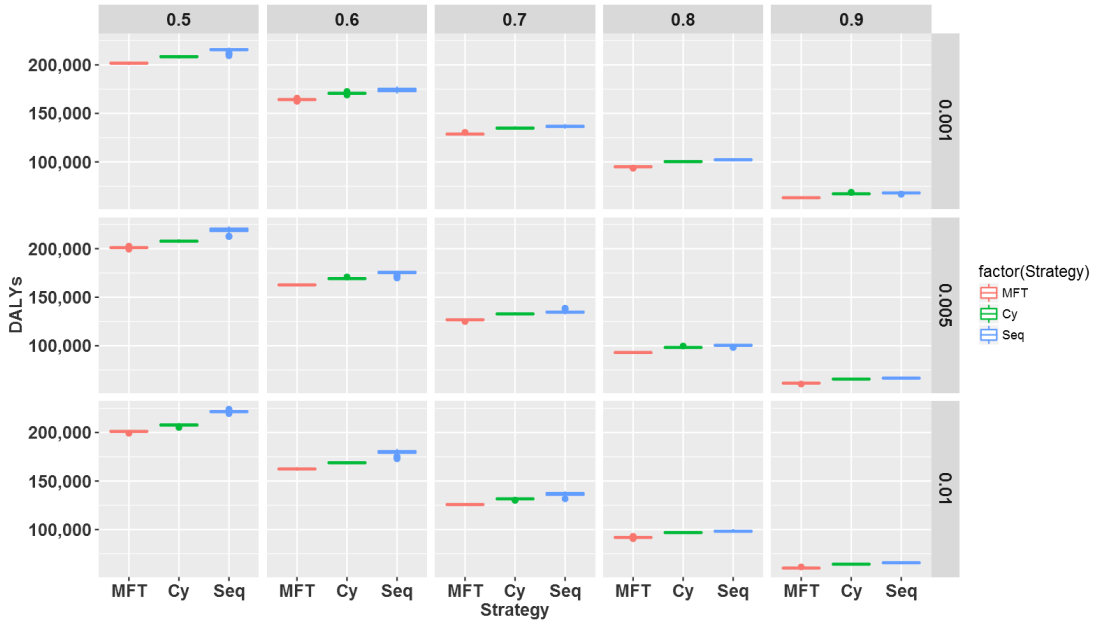


Figure 5-5: The mean disability adjusted life years (DALYs) for different strategies, different costs of resistance (C_R), and different treatment coverages (f) in a low-transmission setting with an EIR of 1·3 for the top graph, and a high transmission setting with an EIR of 20.3 for the bottom graph. The y-axis represents the DALYs and the x-axis shows the strategies which are MFT strategy (MFT), cycling (Cy) and Sequential strategy (Seq). Each column shows the predicted DALYs for a population of 1 million people during 20 years with bars spanning the IQR of 100 model simulations. The DALYs are lower for multiple first-line therapies than for cycling or sequential strategies. The DALYs exhibit narrow distribution across all the scenarios. The DALYs comprise the years life lost (YLLs) and the years lived with disability (YLDs).

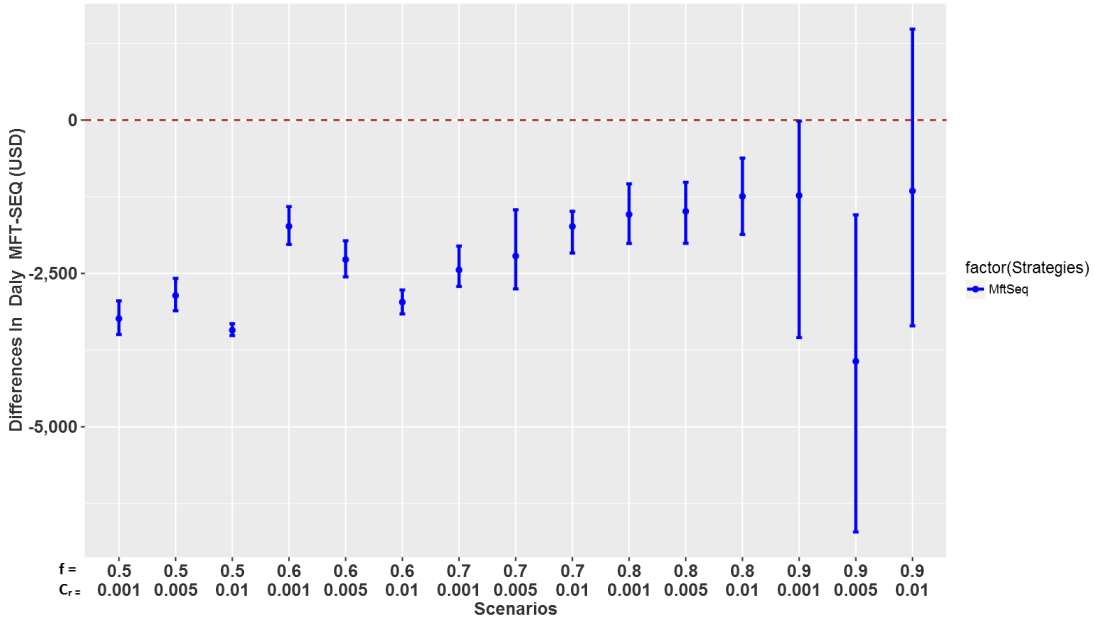
5.3.2.2 Differences in DALYs with 95% confidence intervals

Figure 5-6 illustrates the number of discounted DALYs averted by the MFT strategy compared with the sequential strategy or the cycling strategy for a total population of 1 million people over 20 years in low transmission settings. When compared to the sequential strategy, the MFT strategy resulted in a mean estimated health benefit of 1,204 DALYs averted (95% CI -1,832 to -609) at 90% treatment coverage and 1%

fitness costs and 3,206 DALYs averted (95% CI-3,453 to -2,910) at 50% treatment coverage and 0.1% fitness cost in a low transmission setting. The health benefit of all the strategies increases with treatment coverage. The differences in DALYs were not significant between scenarios using the bootstrapped methods at 90% treatment coverage and 1% fitness cost (Figure 5-6 graph 1). When the prevalence was low (EIR ≤ 1.33), the treatment coverage was high (90%) and the cost of resistance was high (1%), the MFT strategy still averted more cases and more treatment failures than the cycling/sequential strategy, resulting in the lowest DALYs. Nevertheless more parasite populations were driven to elimination when treatment coverage was high (f=90%). As a result, the majority of simulations in this scenario reached extinction. The MFT strategy still averted more cases and deaths than the cycling/sequential strategies but the differences in cases and deaths were smaller than the other scenarios. As a result the differences in DALYs were not sufficiently large enough to achieve the 95% significance test (Figure 5-6 graph 1). The differences in DALYs between the MFT strategy and sequential strategy were significant for all the scenarios under a high transmission setting (EIR ≤ 20.33). This reflects the fact that MFT strategy worked better in a high transmission setting than in a low transmission setting as it averted more malaria cases and deaths.

When compared to the cycling strategy, the estimated mean health benefit of the MFT strategy versus the cycling strategy was between 6,571 DALYs averted (95% CI-6,867 to -6,236) at 50% treatment coverage and 1% fitness cost an 3,886 DALYs averted (95% CI-4,073 to -3,681) at 90% treatment coverage and 1% fitness cost. The MFT

strategy averted more DALYs than the cycling strategy for all the scenarios although the differences in DALYs were not significant in settings with high treatment coverage (>80%) in a low transmission setting (Figure 5-6 graph 2). The cycling strategy was superior to the sequential strategy in terms of DALYs. The differences in DALYs between the MFT strategy and cycling strategy were significant for all the scenarios under a high transmission setting (EIR ≤ 20.33). The next section is going to focus on the cost-effectiveness results for two pairs of comparison: MFT strategy versus sequential strategy, and MFT strategy versus cycling strategy.



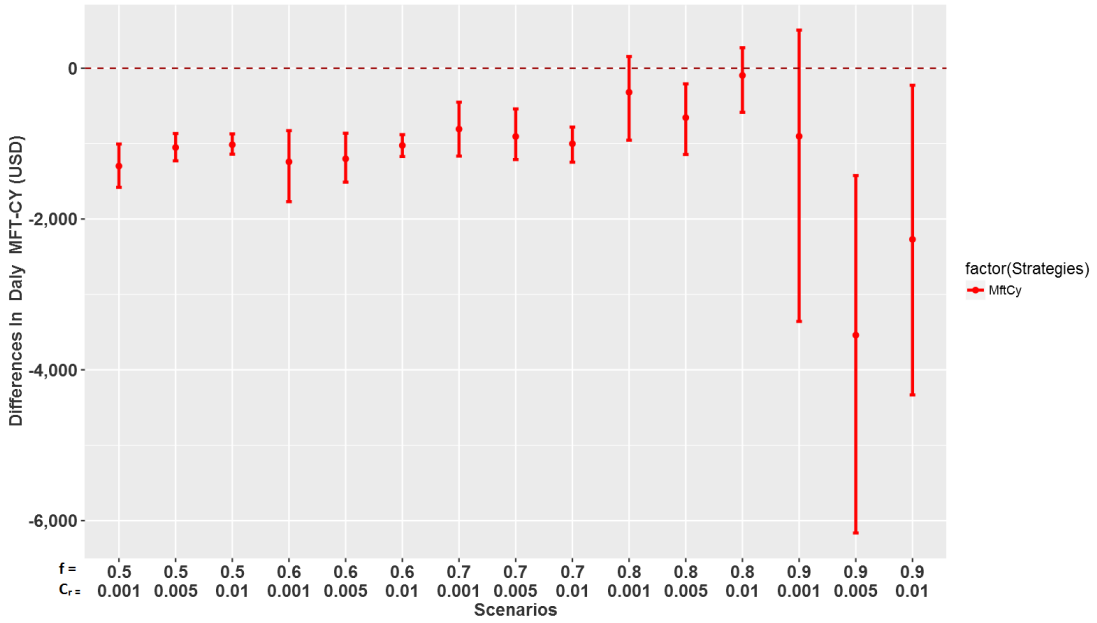


Figure 5-6: The mean differences in DALYs with 95% confidence intervals for the MFT strategy and sequential strategy (the first graph) and between the MFT strategy and the cycling strategy (the second graph) across different costs of resistance (CR), and different treatment coverages (f) in a low transmission setting with an entomological inoculation rate of 20·3. The x-axis represents the differences in DALYs between strategies being compared. The y-axis represents the 15 different scenarios corresponding to different treatment coverage levels (50% to 60% to 70% to 80% to 90%), and different biological fitness costs for drug-resistant genotypes (0.1% 0.5% 1%) from left to right in the graph. These results were based on the 1000 bootstrapped and probabilistic simulations of differences in DALYs. The dot represents the median difference in accumulative and discounted DALYs per 1 million population during the 20-year simulation spanning with 95% credible range. The colours of the dots represent the pair of strategies being compared which are MFT strategy versus the sequential strategy (blue), strategy versus the cycling strategy (red) The red dash line indicates the mean differences in DALYs between strategies were negligible. The dots and the 95% credible range lie below the red dash line indicate the MFT strategy was associated with significantly higher effectiveness and vice versa.

5.3.3 **Cost-effectiveness results**

5.3.3.1 Incremental cost-effectiveness results

Using the ICER formula presented earlier, the incremental cost- effectiveness ratio of the MFT strategy yielded negative ratios indicating in these instances that the MFT

strategy had higher effectiveness at a lower cost than either cycling or sequential strategy, implying that the MFT strategy was the 'dominant' strategy, eventhough it required considerable set-up resources at the beginning. Figure 5-7 shows the cost-effectiveness plans for four scenarios with high treatment coverage (greater than 80%). These 4 scenarios were special because the 1000 simulated differences in costs and DALYs between the MFT strategies versus the cycling/sequential strategy were scattered around widely on both the sides of the diagonal line that corresponds to the WTP threshold of $1,055 per DALYs averted for low income countries. A high proportion of simulations (80% to 90%) of differences in costs and effects lie on the right hand-side of the line, implying that the implementation of the MFT strategy ought to be considered cost-effective. The remaining proportion (10% to 20%) of the simulations on the left-hand side of the line supported the comparators which was the single first-line strategies because the MFT strategy exceeded the decision makers of $1,055 per DALYs averted for low income countries.

For the other 26 scenarios, all of the dots or simulations lie on the right bottom quadrant of the cost-effectiveness plane meaning that the MFT strategy was associated with lower costs and lower DALYs (higher effectiveness) than the single first-line strategies with 100% certainty. In these scenarios, the MFT strategy was always an optimal choice across all WTP values.

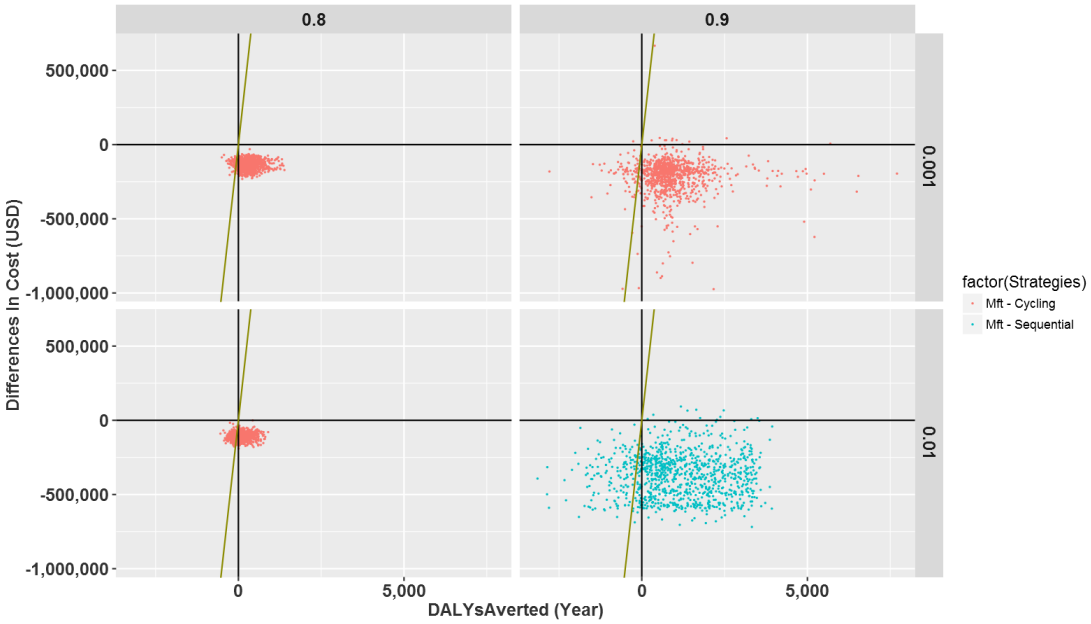


Figure 5-7: Cost-effectiveness plane: the MFT strategy versus the 5 year cycling strategy (red) or the MFT strategy versus the sequential strategy (green), obtained through the bootstrapped analysis in low transmission settings of 1.3 infectious bites per person per year. The figure contains 4 different scenarios corresponding to different treatment coverage levels (80% to 90%), and different biological fitness costs for drug-resistant genotypes (0.1% to 1%) from left to right in the panels. The graph represents 1,000 bootstrapped simulations of the incremental cost-effectiveness ratio (ICER) (dots) with respect to its components: differences in DALYs averted on x-axis and incremental costs per million individual on y-axis. The diagonal line represents the decision marker's willingness to pay of US$1,005 per DALY averted for low transmission settings. Points below the diagonal line represent simulations in which MFT strategy was a cost –effective strategy at a threshold of US$1,005 per DALY averted. The other 26 groups were not shown because they demonstrated that the MFT strategy achieved 100% cost-effectiveness.

5.3.3.2 Cost-effectiveness acceptability curves (CEAC)

In 11 of the 15 scenarios MFT dominated the other strategies and was therefore cost-effective at all WTP thresholds. Figure 5-8presents the CEACs for the four scenarios with high treatment coverage (greater than 80%) where MFT was not always the dominant strategy. These graphs show that the probability of the MFT strategy

relative to sequential strategy or cycling strategy being cost-effective could not achieve 100% as in other 11 scenarios in low but varied approximately around 80% to 90% in a low transmission setting. All the simulations indicated that the MFT strategy was even better if implementing in the high transmission setting.

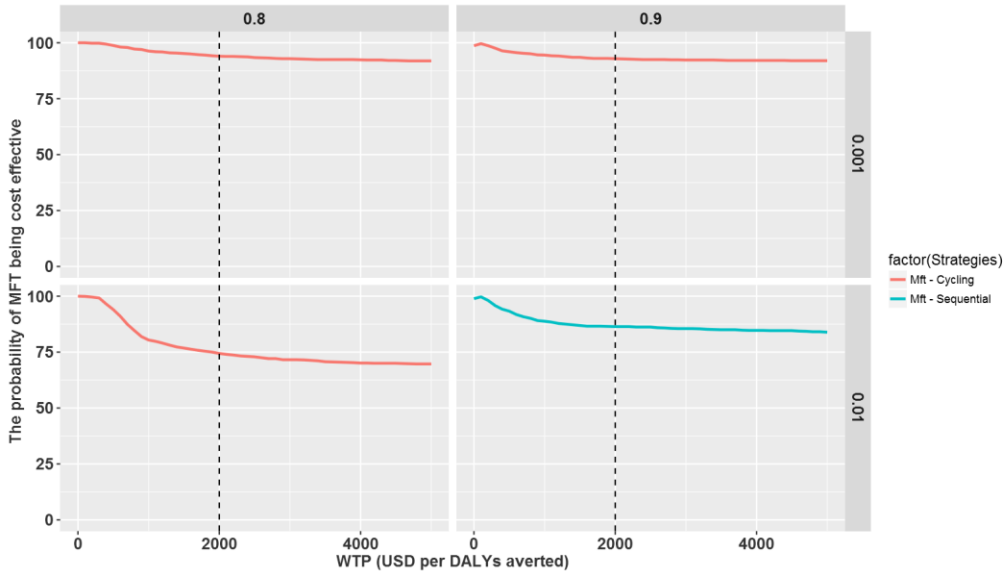


Figure 5-8:Cost-effectiveness acceptability curves (CEACs) for MFT strategy compared to the 5 year cycling (green) and the sequential strategy (red) in a low transmission settings of 1.3 infectious bites per person per year The figure contains 4 different scenarios corresponding to different treatment coverage levels (80% to 90%), and different biological fitness costs for drug-resistant genotypes (0.1% to 1%) from left to right in the panels. These four scenarios were shown because the MFT strategy did not achieve 100% cost-effectiveness relative to single first-line drugs in these scenarios. The acceptability curve was constructed by plotting the cumulative distribution of the incremental cost-effectiveness ratio (ICER) of MFT strategy compared with 5 year cycling or sequential strategy per DALYs averted. The y-axis represents the probability of the MFT strategy being the most cost-effective option for every level of policy makers' willingness-to-pay for each DALY averted (x-axis). The dashed line correspond to the willingness-to-pay at US$1,005 per DALY averted. Each probability is calculated as a proportion of 1000 simulations where the incremental cost-effectiveness ratio (ICER) is less than the ceiling ratio. When the number of DALYs averted is negative, the ICER is assigned a value higher than the ceiling ratio to avoid classifying these simulations as cost-effective. At willingness-to-pay (WTP)

of $1,005 per QALYs, the CEAC determines that the MFT strategy is the most cost-effective option compared to the 5 year cycling strategy and sequential strategy.

5.3.3.3 One-way sensitivity analysis

To reflect the different drug policy and implementation strategies, uncertainty around the key costs of the MFT strategy (the training costs, the drug costs, the M/E costs) and the key epidemiological parameters (the probability of early treatment failures leading to severe malaria (P3), the probability of untreated malaria case progressing to severe malaria (P4), the probability of severe malaria patients obtaining inpatient care (P5)was examined individually in one-way sensitivity analyses. Figure 5-9 shows that when the key costs of the MFT strategy (the training costs, the drug costs, the M/E costs) fluctuated +/-20%, the NMB values of the MFT strategy in relation to the sequential strategy varied only minimally between -/+1% to -/+4%.The MFT strategy remained the most cost-effective even when its key costs were20% higher than in the base case. The results of this sensitivity analysis suggested that the cost-effectiveness results of the MFT strategy remained robust to plausible variations of the main cost assumptions used in the model. The same conclusion was applied for the comparison between the perfect MFT strategy and cycling strategy. The three key epidemiological parameters were important determinants of the results, causing a variation between 6% to 20%.

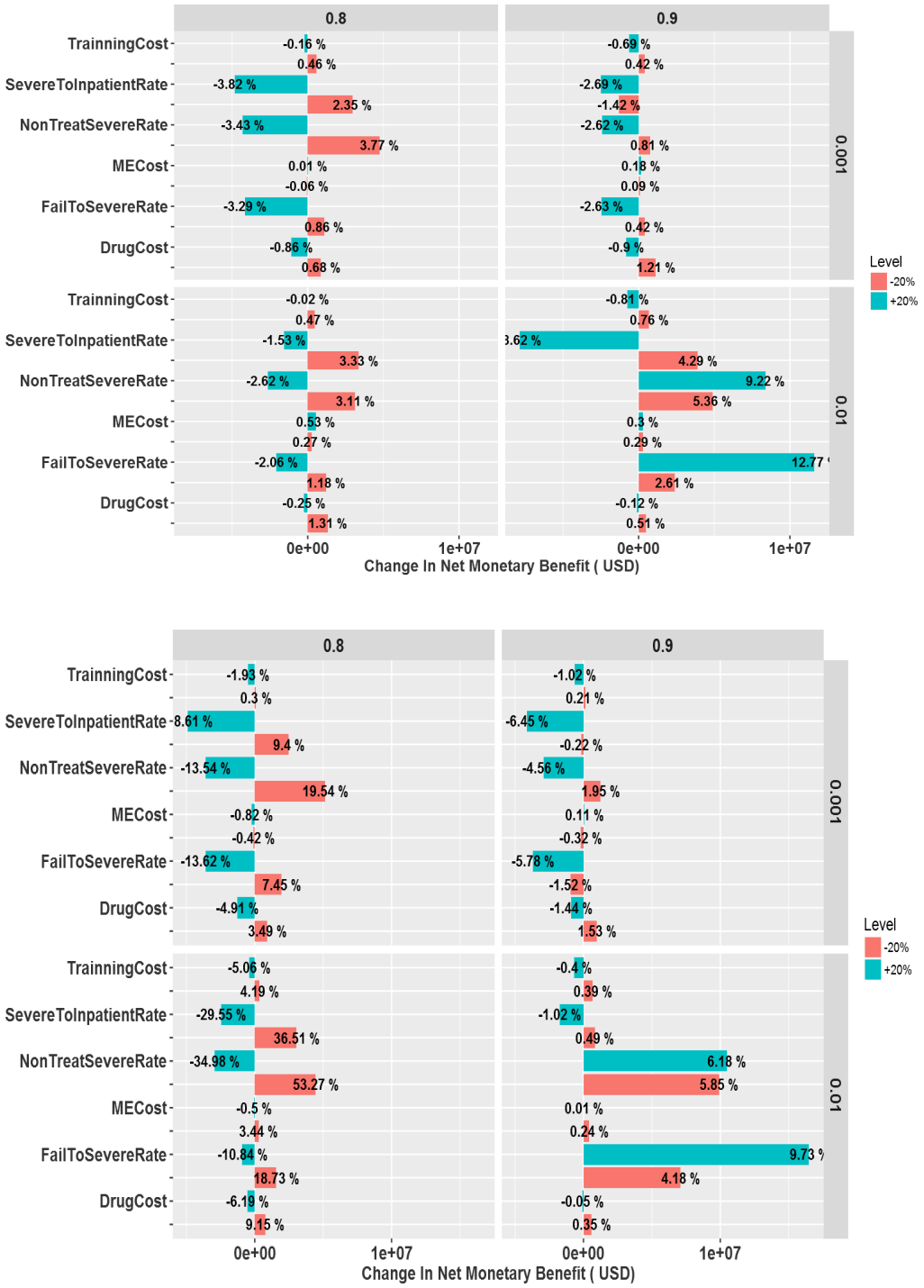


Figure 5-9: Tornado diagram of one-way sensitivity analysis results for net monetary benefits (NMBs) of the MFT strategy versus the sequential strategy (top graph) and the MFT strategy versus the cycling strategy (bottom graph) associated with range of each parameter in a low transmission setting (1.3 infectious bites per person per year). This graph contains 4special scenarios corresponding to different treatment coverage levels

(80% to 90%), and different biological fitness costs for drug-resistant genotypes (0.1% to 1%) from left to right in the panels. This sensitivity analysis presented in this table was done at WTP of US$1,005. The x-axis corresponds to the estimated NMBs of the MFT strategy relative to the sequential strategy. The y-axis shows the single parameters that are being varied between a low to a high range based on the 95% confidence interval of the parameter estimate where available and a 20% range where a confidence interval was not available. The red bars represent the low value of each main parameter that are being varied as listed previously; the green bars represent the high value. Bar to the right represent more favourable for the cost-effectiveness of the MFT strategy.

5.3.3.4 Expected value of perfect information (EVPI)

The previous analysis concluded that perfect MFT strategy has a high probability of being the dominant strategy, saving costs and yielding higher health benefits than the comparator strategies. This part presents the EVPI which is defined as the value of collecting additional information to eliminate or reduce all uncertainty on all parameters involved in taking a decision that would affect the modelled population of 1 million individuals over 20 years. In the low transmission setting, the EPVIs were negligible for treatment coverage $\leq$ 80% indicating that our choice of adopting the perfect MFT strategy as the first-line drug policy is the optimal decision and there is no economic justification for conducting further research. As demonstrated earlier, in the remaining scenarios the MFT strategy dominated the sequential strategy with the probability of 80%, however there were 20% chance that the sequential strategy could be more cost-effective than the perfect MFT strategy. Figure 5-10 presents the EVPI for four different scenarios with high treatment coverage (greater than 80%) as a function of the WTP values for different treatment coverage levels and fitness cost of resistance in a low transmission setting. As treatment coverage approached 90% and fitness cost varied around 0.1% or 1%, the EPVIs recommended an investment of up

to $800,000 at WTP for a DALY averted of $1,005 for further research to eliminate all uncertainty involved in the decision of adopting the MFT strategy. As for the high transmission setting, the perfect MFT strategy was the optimal decision at all values of WTPs therefore the EVPIs were negligible across all the scenarios.

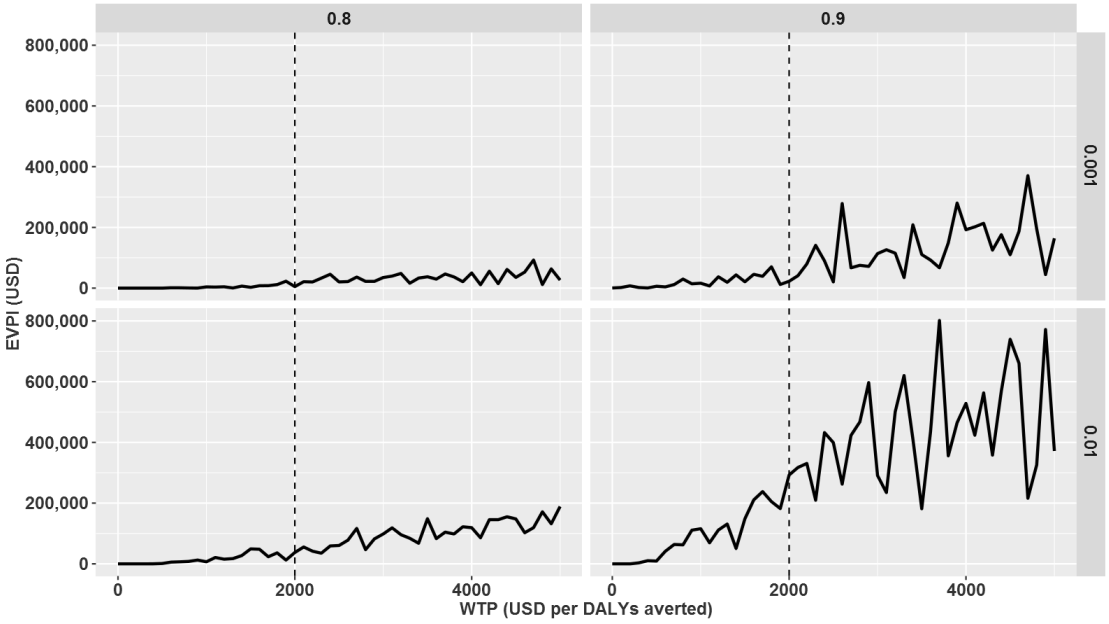


Figure 5-10: Expected value of perfect information (EVPI) of the MFT strategy versus cycling or sequential strategy in a low transmission setting of 1.3 infectious bites per person per year. The figure contains 4 different scenarios corresponding to different treatment coverage levels (80% to 90%), and different biological fitness costs for drug-resistant genotypes (0.1% to 1%) from left to right in the panels. The x-axis axis represents the decision maker's willingness to pay ranging from 0$ to $5000. The y-axis represents the EVPI for a population of 1 million persons for 20 years, discounted at 3% per annum. The dashed line corresponds to the ICER threshold of $1,055 per DALY averted. In the scenario of treatment coverage at 90% and fitness cost of resistance at 0.1%, the EVPI per 1 million people was arguably large, rising from $1 to $2 million at WTP for a DALY averted of $0 and $1,005 respectively.

5.3.3.5 Threshold analysis for the drug costs of the MFT strategy

Table 5-6 and 5-7 show the results of the threshold analysis to determine at which drug price per treatment course of the MFT strategy (including the drug purchase and the cost of drug delivery) the total costs of this strategy is equivalent to the total cost the sequential strategy; or the probability that the MFT strategy is cost-effective (where it has more than 50% probability of being cost-effective as compared with cycling or sequential strategies).

In a low transmission setting, the drug price per treatment course of the MFT strategy would have to increase by as much as 1800% for the total costs of the MFT strategy to be equivalent to the total cost of sequential strategy. For the second criteria, the drug price per treatment course would have to increase by 2700% in the scenarios which the treatment coverage less than 90% for there to be less than a 50% probability of MFT being more cost-effective than the sequential strategy. In high transmission, the increase in the drug price of the MFT strategy would have to exceed 3000% before the probability of it being cost-effectiveness was less than 50% as compared with the sequential strategy.

For the comparison between the MFT strategies versus the cycling strategy, the drug price of MFT strategy would have to increase by up to 400% to be equivalent to the cost of cycling strategy. In the high transmission setting, the drug price of the MFT strategy would have to increase by 2000% with treatment coverage less than 50% for it to be less likely to be cost-effective than the cycling strategy.

Table 5-6: Absolute increase of drug costs of MFT strategy relative to sequential strategy across treatment coverage (50%, 60%, 70%, 80%, 90%) and fitness cost of resistance (0.001, 0.005, 0.01)

Treatment coverage	Fitness cost	Low transmission settings		High transmission settings	
		Criteria 1	Criteria 2	Criteria 1	Criteria 2
50%	0.001	4	53	2	40
50%	0.005	2	47	1	53
50%	0.01	4	57	2	58
60%	0.001	2	27	2	24
60%	0.005	4	36	2	32
60%	0.01	2	49	2	42
70%	0.001	4	35	2	17
70%	0.005	2	36	2	18
70%	0.01	4	31	2	25
80%	0.001	3	23	1	14
80%	0.005	5	26	2	15
80%	0.01	13	25	2	13
90%	0.001	18	23	2	9
90%	0.005	11	171	2	10
90%	0.01	11	78	2	11

Table 5-7: Absolute increase of drug costs of MFT strategy relative to cycling strategy across treatment coverage (50%, 60%, 70%, 80%, 90%) and fitness cost of resistance (0.001, 0.005, 0.01)

Treatment coverage	Fitness cost	Low transmission settings		High transmission settings	
		Criteria 1	Criteria 2	Criteria 1	Criteria 2
50%	0.001	2	22	1	20
50%	0.005	4	19	2	20
50%	0.01	2	18	1	20
60%	0.001	3	19	2	16
60%	0.005	2	19	1	16
60%	0.01	2	18	2	16
70%	0.001	2	12	1	13
70%	0.005	3	14	2	14
70%	0.01	2	18	1	13
80%	0.001	3	6	2	10
80%	0.005	2	12	1	11
80%	0.01	4	3	2	10
90%	0.001	2	16	1	7
90%	0.005	4	151	2	8
90%	0.01	2	146	1	8

5.3.4 **Application to Vietnamese setting**

The model is adapted to a low and high transmission setting that resemble the Vietnamese and Tanzanian settings, but this is still an abstraction that is not fully parameterized to these contexts, therefore I chose not to state that these results are specific for either country. Doing so was not feasible as there are many other contextual factors that would determine the impact of MFT strategy such as the geographical distribution of malaria cases and how the different antimalarials were allocated to optimize the impact of the MFT strategy. This limitation was also true for the OUCRU IBM model and addressing this would be beyond what I could reasonably achieve in this thesis. Despite these limitations both the models offer important and much needed insights about the potential role and cost-effectiveness of the MFT strategy. As the history of antimalarial control has shown that resistance to CQ and then to SP first emerged in Cambodia and spread to sub-Saharan Africa in 2 or 3 years after the resistance emergence, rendering important efforts in the fight against *falciparum* malaria ineffective [173,236–238]. Now we witness the history might repeat this story again. The resistance to the *artemisinin*-current first-line drugs has emerged in Cambodia in 2009 [233] and has spread throughout the Delta Mekong river during 2013 [234] and it is likely to spread to Africa and on a global soon.

Artemisinin has played an important role in the control of malaria worldwide. The prospect that Plasmodium parasites can develop complete resistance to *artemisinin* derivatives could be a catastrophe for global health. Currently, there are no drugs in the pipeline to replace *artemisinin,* and it could take five or more years to find a replacement drugs [189] . The health decision makers all over the world needs to act

quickly to delay the development of this drug resistance. The OUCRU IBM model has demonstrated the MFT strategy is effective in delaying the resistance emergence and the development of resistance in various settings of epidemiological factors. The OUCRU IBM shows the MFT strategy yielded fewer treatment failures, shorter time to 1% resistance emergence compared to single first-line strategies [221,235] that were status-quo strategies in African countries and Vietnam. However, as Maude and Lubell et al (2010) [192] stated that the choice of strategy for use would likely be heavily influenced by cost and affordability. Highly effective strategies for malaria control measures may be economically inefficient. Nevertheless in this thesis, I have demonstrated that the MFT strategy was a cost-effective strategy across a wide range of economic and epidemiology factors and should be implemented on a wide scale at the global level as this strategy cost less and averted more DALYs compared to single first-line drugs.

The model is therefore supposed to mimic a low-transmission setting (EIR=1.3) and that this can be any non-specific setting. It is not "supposed to be" Africa or Vietnam or anywhere else. It is just a hypothetical location. In the following analysis, the model was run for a low transmission setting and used Vietnam-specific costs (Table 5-8) to evaluate the full economic cost and the cost-effectiveness of the MFT strategy versus the cycling or sequential strategy.

The OUCRU-IBM model were rerun to produce the outputs under the scenarios that had EIR <1.3, treatment coverage =90% and the fitness cost of resistance = 0.01% to 0.1%. The case management model was also rerun to incorporate the updated cost of policy change and the treatment costs specific for Vietnamese setting. The search for

drug delivery cost in Vietnam resulted in zero. This analysis decided to use the estimates of the delivery cost of routine vaccine in national services in Vietnam [236]. This paper found that a delivered dose of vaccine made up of 24% of vaccine price after the introduction of pentavalent vaccine.

As for the treatment costs, a study in Vietnam [237]presents an estimation of the direct economic costs and indirect costs of reduced productivity of a malaria episode at a total of 11.79 USD (2005 prices) to households in the mountainous and forested province of Ninh Thuan. As for the DALYs and transition probabilities, these values in low transmissions in Table 5-2 and 5-4 were selected. The Vietnam GDP per capita in 2013 of $2,000 was used as WHO's guidelines in 2003[14]

Table 5-8: The cost parameters for Vietnamese setting:

Activities	**Unit cost for strategies**				**References for unit costs**
	Cycling/ Sequential strategy	**MFT strategy**		**Distribution**	
		Unit cost (range)	Percent increase over single first-line drugs		
Set-up costs (non-recurrent costs)					

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	MFT strategy		Distribution	
		Unit cost (range)	Percent increase over single first-line drugs		
Activity 1: Policy formulation: This includes activities such as planning, policy related consultations and advisory meetings, consensus building	2,965 (+ - 20%)	5,803 (+/- 20%)	100%	Triangle	For the cycling/sequential strategy, the costs of activity 1 were substituted by the costs of the project team recruitment, consultation and planning $2,965 per year (2% of the average costs of $62,092 and $234,397 in Table 4-1) These values ($62,092 and $234,397) were derived from the costs of the switch from CV8 or artesunate-primaquine to CV8 or DHA-PPQ in 2007 and to DHA-PPQ completely in 2009 in Vietnam [211,212] For MFT strategy, the costs of the project team recruitment, consultation and planning were increased to $5,803 per year (3% of $193,423 in Table 4-1). This value ($193,423) was derived from the costs of the switch from CQ to CV8 or artesunate-primaquine in Vietnam in 2003 [210]
Activity2: Revision & production &printing & distribution of IEC, drug packages and health materials .	0.00016 (min=0.00008 max = 0.0002)	0.001 (+/- 20%)	525%	Triangle	For cycling and sequential strategy, the costs of activity 2 were equal to $0.00016 (0.00008 to 0.0002) per person per year. The average costs of the revision and printing from the switch from CV8 or artesunate-primaquine to CV8 or DHA-PPQ in 2007 and to DHA-PPQ completely in 2009 in Vietnam [211,212] (Table 4-2) For the MFT strategy, the cost of printing and revision associated with the cycling

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	MFT strategy		Distribution	
		Unit cost (range)	Percent increase over single first-line drugs		
					and sequential strategy was $0.001 per person per year. This value $0.001 was derived from the costs of the switch from CQ to CV8 or artesunate-primaquine in Vietnam in 2003 [210]
Activity 3: Training of health personnel -Training health personnel in formal health facilities	0.00096 (min = 0.0005 max = 0.0014)	0.007 (+/- 20%)	629%	Triangle	For cycling and sequential strategy, the training cost per person (including training of health personnels, trainers and supervisors) was equal to $0.00096 (0.0005 to 0.0014) per person per year. The average costs of the revision and printing from the switch from CV8 or artesunate-primaquine to CV8 or DHA-PPQ in 2007 and to DHA-PPQ completely in 2009 in Vietnam [211,212] (Table 4-2) For MFT strategy, the cost of training health personnels was equal to $0.007 per person per year. This value $0.007 was derived from the costs of the switch from CQ to CV8 or artesunate-primaquine in Vietnam in 2003 [210]
Activity 4: Information, education, and communication (IEC).	0.001 (+/- 20%)	0.003 (+/- 20%)	200%	Triangle	For cycling and sequential strategy, the cost of IEC were equal to 0.001 per person per year. This value was derived from the costs of the switch from CV8 or artesunate-primaquine to CV8 or DHA-PPQ in 2007 [211] For MFT strategy, the cost per person was $0.003 per

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	MFT strategy		Distribution	
		Unit cost (range)	Percent increase over single first-line drugs		
					person per year which was obtained from the costs of the switch from CV8 or DHA-PPQ to completely DHA-PPQ in 2009 [212]
Activity 5:Program management and monitoring and evaluation (M/M&E)	0.0004 (+/- 20%)	0.0012 (+/- 20%)	200%	Triangle	For cycling and sequential strategy, the cost of program management and monitoring were equal to $0.0004. This value was derived from the costs of the switch from CV8 or artesunate-primaquine to CV8 or DHA-PPQ to in 2007 [211] For MFT strategy, the cost per person was equal to $0.0012 per person per year. This value was derived from the costs of the switch from CQ to CV8 or artesunate-primaquine in 2003 [210]
Recurrent costs					
Activity 6: **Drug purchase** Volume discount	1% per 100,000 doses	0.3% per 100,000 doses (+/- 20%)		Triangle	A volume discount is reduced to a third if the drug assortment for a treatment is increased to 3 drugs. [179]
Drug delivery costs per uncomplicated case (including storage, distribution, training, and management) from the central-level to health facilities-level	24% of the drug price	48% of the drug price	100%	Triangle	For cycling/sequential strategy, the cost of delivering the drugs was assumed to be 24% of the drug price. This is the average cost of delivering routine vaccines after the introduction of pentavalent vaccine from the central-level to health facilities level in Vietnam [236]. For MFT strategy, the cost of delivering drugs was assumed to double the cost

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	MFT strategy		Distribution	
		Unit cost (range)	Percent increase over single first-line drugs		
					of delivering drugs in the cycling/sequential strategy.
Activity 7: **Case-management** Direct costs of an uncomplicated malaria case at formal-sector facilities The cost of second line treatment The average costs of treating adult severe case (>5 years old) and children severe case (≤ 5 years old)	11.79 (range 7.48 to 14.27) 21 54.31 (22.20 to 202.32)			Triangle Fixed value Triangle	These costs of outpatient visit included an outpatient consultant, and the patient cost such as travel costs, medical supplies, non-medical supplies ($0.69) (excluding fixed costs and drug costs) plus the mean weighted productivity losses by age for all symptomatic cases ($11.10) (2005 USD) [237] The cost of second-line quinine is 16.32 (2009 USD) or 21 (2013 USD) [174] 54.31 (22.20 to 202.32) (2005 USD) is the average economic cost of treating a 10-day episode for a family of five with two children under 10 and the total estimated treatment cost per severe episode at hospital level in Vietnam [237,238]

5.3.4.1 Results:

5.3.4.1.1 The total costs for strategies in the Vietnamese setting

Figure 5-11 shows that the implementation of the MFT strategy was associated with an average cost ranging from the lowest value of $306,524 (at 90% treatment coverage and 1% fitness cost) to the highest value of $663,303 (at 90% treatment coverage and 0.1% fitness cost). The MFT strategy was the cheapest strategy compared to the single

first-line strategies across 3 combinations of the fitness cost levels and values of treatment coverage. The MFT strategy was preferred at all levels of fitness costs of resistance in low transmission settings (EIR< 1.3).

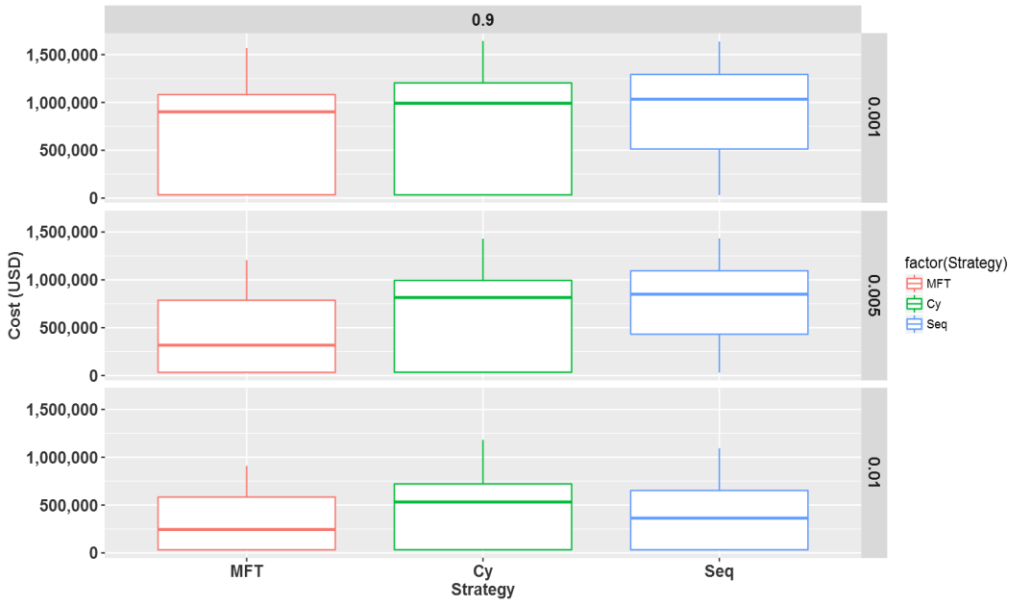


Figure 5-11: Mean discounted total cost per 1 million persons for different strategies, different costs of resistance (C_R), and different treatment coverages (f) in a low-transmission setting with an entomological inoculation rate of 1.3, treatment coverage of 90%. Each row shows the three values of fitness cost of resistance (0.1% , 0.5% 1%). The costs are in 2013 US dollars. The y-axis represents the costs in US dollars and the x-axis shows the strategies which are MFT, cycling (Cy) and Sequential strategy (Seq). The y axis represents the mean total costs results of 100 model simulations with bars spanning the IQR. The total costs are lower for multiple first-line therapies than for cycling or sequential strategies across different scenarios.

5.3.4.1.2 **The impact of health outcomes (DALYs) in the Vietnamese setting**

Figure 5-12 illustrates that for the low transmission settings, the probabilistic simulations suggested that the MFT strategy resulted in the largest reduction of DALYs across different coverage levels of treatment, and fitness cost of resistance

values in both low/high transmission settings. The MFT strategy was associated with an average DALYs 2,797 DALYs at treatment coverage of 90% and fitness cost of resistance of 1% to 5,419 DALYs at treatment coverage of 90% and fitness cost of resistance of 0.1% per 1 million population. The MFT strategy incurred significantly less DALYs than both of the single first-line strategies at 95% confidence intervals according to the bootstrapping method.

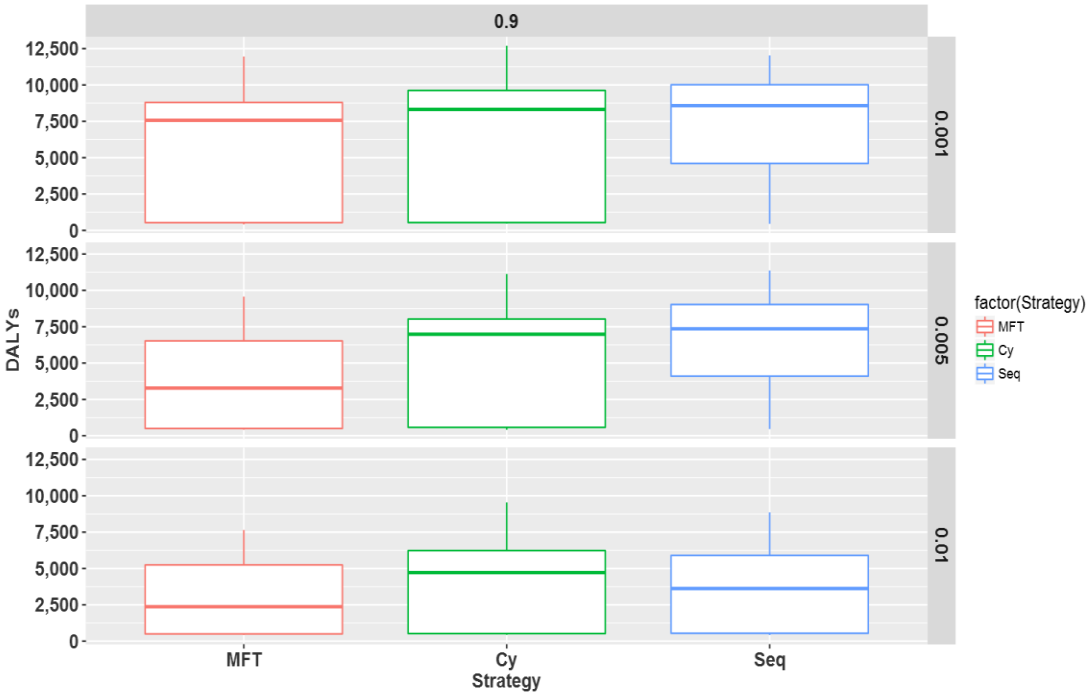


Figure 5-12: Mean discounted disability adjusted life years for different strategies, different costs of resistance (C_R), and different treatment coverages (f) in a low-transmission setting with an entomological inoculation rate of 1.3, treatment coverage of 90%. Each row shows the three values of fitness cost of resistance (0.1% , 0.5% 1%). The y-axis represents discounted DALYs in US dollars and the x-axis shows the strategies which are MFT, cycling (Cy) and Sequential strategy (Seq). The y axis represents the mean discounted DALYs results of 100 model simulations with bars spanning the IQR. The total costs are lower for multiple first-line therapies than for cycling or sequential strategies across different scenarios.

5.3.4.1.3 **Cost-effectiveness results of MFT strategy for Vietnamese settings**

Figure 5-13 shows that in 3 scenarios MFT dominated the other strategies and was therefore cost-effective at all WTP thresholds. These graphs show that the probability of the MFT strategy relative to sequential strategy or cycling strategy being cost-effective could not achieve 100% but always exceed 75% at Vietnamese willingness to pay for each DALY averted at $2000. The results of EVPI, threshold analysis and one-way sensitivity were similar as in the original analysis. These findings will be disclosed on request.

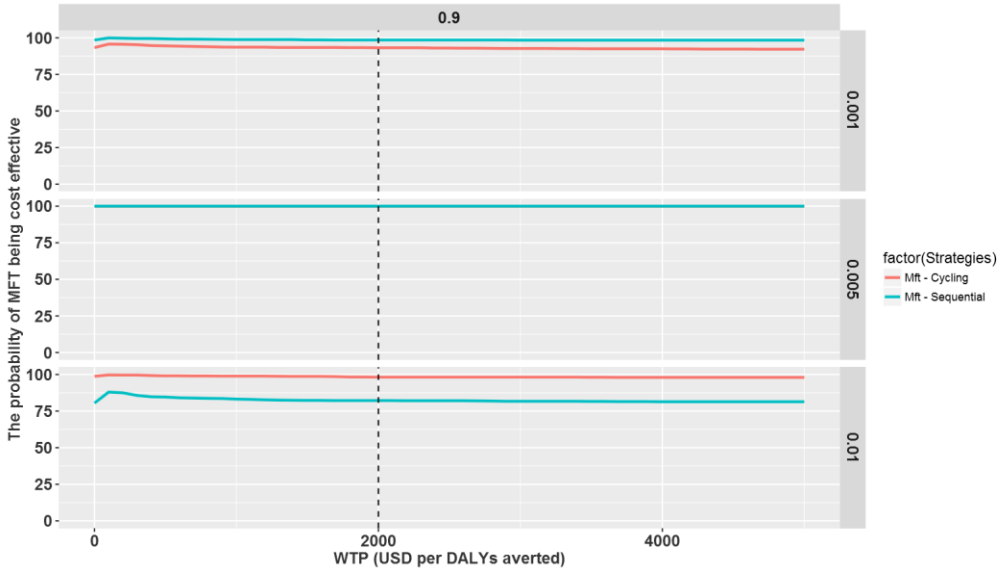


Figure 5-13: Cost-effectiveness acceptability curves (CEACs) for MFT strategy compared to the 5 year cycling (green) and the sequential strategy (red) in a low transmission settings of 1.3 infectious bites per person per year. The figure contains 3 different scenarios corresponding to different biological fitness costs for drug-resistant genotypes (0.1% to 1%) The acceptability curve was constructed by plotting the cumulative distribution of the incremental cost-effectiveness ratio (ICER) of MFT strategy compared with 5 year cycling or sequential strategy per DALYs averted. The y-axis represents the probability of the MFT strategy being the most cost-effective option for every level of Vietnamese policy makers' willingness-to-pay for each DALY averted (x-axis). The dashed line correspond to the Vietnamese willingness-to-pay at US$2,000 per DALY averted. Each probability is calculated as a proportion of 1000 simulations where the incremental cost-effectiveness ratio (ICER) is less than the ceiling ratio.

5.3.4.1.4 **EVPI of MFT strategy for Vietnamese settings**

Figure 5-14 presents the EVPI for four different scenarios with high treatment coverage (greater than 90%) as a function of the WTP values and fitness cost of resistance in a low transmission setting. As treatment coverage approached 90% and fitness cost varied around 0.1% or 1%, the EPVIs recommended an investment of up to $800,000 at WTP for a DALY averted of $2,000 for further research to eliminate all uncertainty involved in the decision of adopting the MFT strategy. At the fitness cost of resistance of 0.5%, the perfect MFT strategy was the optimal decision at all values of WTPs therefore the EVPIs were negligible across all the scenarios.

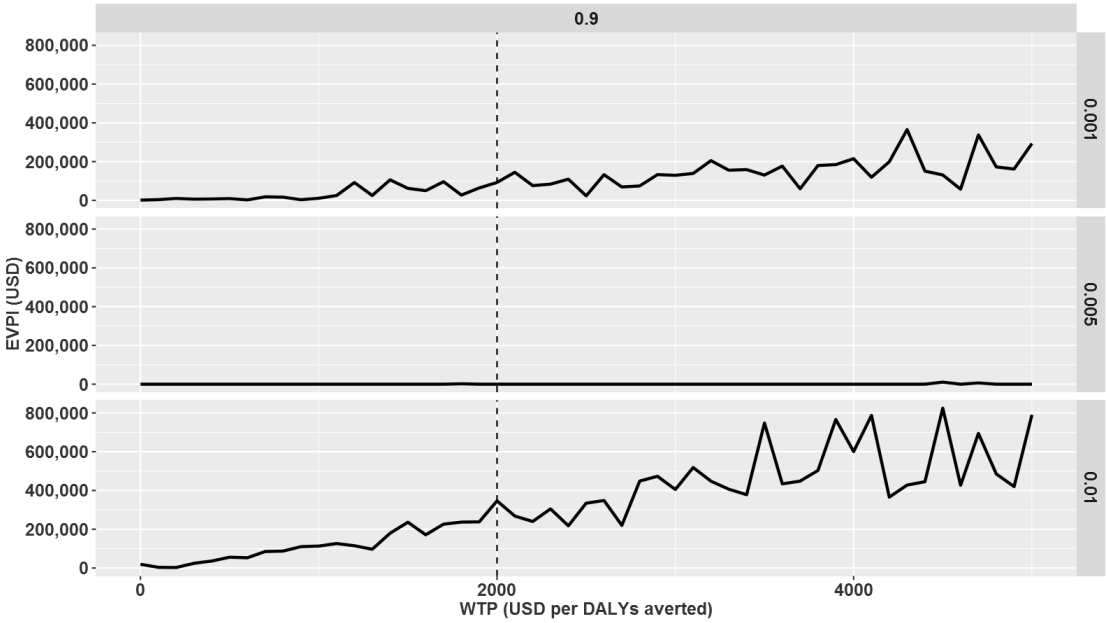


Figure 5-14: Expected value of perfect information (EVPI) of the MFT strategy versus cycling or sequential strategy in a low transmission setting of 1.3 infectious bites per person per year. The figure contains 3 different scenarios corresponding different biological fitness costs for drug-resistant genotypes (0.1% to 1%) . The x-axis axis represents the decision maker's willingness to pay ranging from 0$ to $5000. The y-axis represents the EVPI for a population of 1 million persons for 20 years, discounted at 3% per annum. The dashed line corresponds to the Vietnamese willingness to pay threshold of $2,000 per DALY averted. In the scenario of treatment coverage at 90%

and fitness cost of resistance at 0.1 and 1%, the EVPI per 1 million people was arguably large, rising from $1 to $10 million at WTP for a DALY averted of $0 and $2,000 respectively

5.3.4.1.5 **Threshold analysis for the drug costs of the MFT strategy in Vietnamese settings**

In a low transmission setting, the drug price per treatment course of the MFT strategy would have to increase by as much as 1100% for the total costs of the MFT strategy to be equivalent to the total cost of sequential strategy. For the second criteria, the drug price per treatment course would have to increase by 1900% to 15800% for there to be less than a 50% probability of MFT being more cost-effective than the sequential strategy. For the comparison between the MFT strategies versus the cycling strategy, the drug price of MFT strategy would have to increase by up to 180% to 1000% to be equivalent to the cost of cycling strategy (Table 5-9)

Table 5-9: Absolute increase of drug costs of MFT strategy relative to sequential strategy across treatment coverage (50%, 60%, 70%, 80%, 90%) and fitness cost of resistance (0.001, 0.005, 0.01)

Treatment coverage	Fitness cost	MFT versus sequential		MFT versus cycling	
		Criteria 1	Criteria 2	Criteria 1	Criteria 2
90%	0.001	11.6	19.9	1.8	14.1
90%	0.005	8.5	158.5	2.1	136.2
90%	0.01	4.1	65.5	10.9	132.8

5.3.4.1.6 **Summary of results for Vietnamese setting**

The modeling framework employed here provides a means of predicting the likely costs and effects associated with implementing the MFT strategy aimed at reducing disease burden associated with drug resistance in a setting using Vietnamese specific cost data. Over the long term, the MFT strategy was significantly cheaper than the

single first-line drugs as this strategy was associated with only one policy change during its implementation period. The model results have demonstrated that implementing the MFT strategies as first-line treatment was more cost-effective than the single first-line strategies over 20 year period across a at 90% treatment coverage and fitness cost of resistance (0.1% , 0.5% , 1%) using the Vietnamese specific costs.

5.4 **Discussion**

5.4.1 **Discussion about cost-effectiveness results**

The model results have demonstrated that implementing the MFT strategies as first-line treatment was more cost-effective than the single first-line strategies over 20 year period across a wide range of scenarios of treatment coverage (50%, 60%, 70%, 80%, 90%), fitness cost of resistance (0.001, 0.05, 0.001) and low and high transmission settings. Over the long term, the MFT strategy was significantly cheaper than the single first-line drugs. The costs savings of the perfect MFT strategy were due to a single policy change at the beginning of the implementation period and lower costs of case management for uncomplicated and severe cases and costs of treatment failures to the healthcare providers. The lower cost of case – management for the MFT strategy could be explained by the fact that the MFT strategy created a variable drug environment therefore the chance that the parasite developed to be a drug resistant parasite was very low in relation to changing to single first-line drugs. The MFT strategy was associated with fewer malaria cases, and fewer treatment failures, and deaths. The MFT strategy experienced high initial set-up cost associated with retraining health workers, monitoring and surveillance and communication and publicity during the first years. This fact might prevent policy makers adopting this strategy as their national drug policy if they are reluctant to place more financial burden for their already constraint health budgets. However, this strategy was associated with only one policy change during its implementation period therefore the costs of setting up policy change were annualised over a much longer theurepatic life of the drug than in the case of implementing single first-line drugs. The MFT strategy

required considerable investment at the beginning in order to realize any future benefits.

Treatment coverage, fitness cost, and transmission settings played important roles in the estimation of cost-effectiveness of the MFT strategy. Higher transmission and fitness cost of resistance reinforce the cost-effectiveness of the MFT strategy. In a low transmission setting of 1.3 infectious mosquito bites per person per year, allowing the treatment coverage reach to 90% led to a small reduction of the cost-effectiveness of the MFT strategy because in this situation the majority of cases had already averted by the passive case management system. Although the MFT strategy averted more cases than the cycling and sequential strategy, the differences were not significant. The cost-effectiveness of the MFT strategy was slightly weaker in scenarios with high treatment coverage (>90%) but the economic support for this strategy is still sustained.

The modeling framework employed here provides a means of predicting the likely costs and effects associated with implementing the MFT strategy aimed at reducing disease burden associated with drug resistance. The percentage differences in costs between the MFT strategies versus the sequential strategy were entirely assumed and varied over a range of fixed values. The modeling approach allowed calculating the threshold value of the drug price at which the MFT strategy would no longer appear cost-effective, for any starting value of single first-line drugs. There was no empirical evidence to inform a judgment of how large the differences in costs would be. At the 50% decision rule, the drug price per treatment course of the MFT strategy needed to increase 20 to 60 times to achieve an equal probability of being cost-effectiveness as the sequential strategy or cycling strategy.

When comparing these results with cost-effectiveness for other malaria control or health interventions with the same perspectives, using our estimated population at risk and the costing assumptions above, the cost of implementing the MFT strategy was associated with $0.1 to $0.3 per person annually which is quite comparable to the cost of other malaria control such as the combination of LLIN and ACT plus other interventions at the primary care level in African countries [239,240]. Furthermore, the cost of implementing MFT strategy was much lower than the cost of introducing vaccination or integrated case management which were estimated at $2 to $5 per person per year while yielding the same level of protection [241–243]. In addition, this analysis included the non-drug cost, which was often ignored in economic analyses. Ignoring the set-up cost could overestimate the cost-effectiveness of treatment strategies as in our analysis these costs made up roughly 20% to 40% of the overall costs.

5.4.2 **Limitations**

These findings should be interpreted with caution. The drug costs of the MFT were assumed to be constant over time. However, the drug prices of the MFT strategy might go down because by introducing more drugs to the market the MFT strategy facilitate competition which helps to reduce drug prices. The decreasing trend of drug costs overtime gives more support for the cost-effectiveness of the MFT strategy.

This modelling framework focused only on the population seeking care through formal inpatient/outpatient facilities. It did not accommodate the range of patient-seeking behaviors in, for example, the private sector. Also, the links between levels of

treatment failure, patient compliance, and overall patterns of drug usage were also dynamic, which was not captured. The efficacy of the MFT strategy may be reduced when implemented in the settings such as sub-Saharan Africa where poor adherence to treatment, underdosing were common issues. For example, approximately 20% to 30% of sick patients seek treatment from private practitioners [244]. People tended to purchase the antimalarial drugs from retail stores because the stores operated closer to homes, and sometimes at lower costs. If the private market was large and the non-ACT drugs (SP or chloroquine) were likely to dominate the market (50 to 70% of the entire market), the effectiveness of the MFT strategy may not work as well. However, this situation were unlikely to happen because the private market tended to offer a wider range of drugs (such as choloroquine, amodiaqunine, sulphadozine, pyrimethamine and quinine) [245], this creates an even more variable drug environment which could help to delay of resistance to ACT.

Secondly, this study assumed that enough ACTs are produced to meet the need of malaria cases for 20 years. However, in reality, shortages in supply in some years are expected and other drugs would be used to treat fevers instead of Acts. This stock out problem coupled with the effect of private market would drive the magnitude of the cost and effectiveness of the MFT strategy to be unpredictable. The drug stock outs in public sector may make patient switch between formal and informal providers to find drugs in the private sectors.

There is little available evidence regarding what feasible system of care delivery for the MFT would be operating in either low or high transmission settings. We developed the model based upon the expert opinions. There have been very little formal modeling

studies taking account of private sector due to its changing and complex nature. As a result most of WHO guidelines are relied on the delivery of care by public healthcare workers making this the relevant approach for economic analysis. Therefore, our study collected data generated from public practice routine health system from various published literature as there was a lack of good data on costs and health outcomes across a wide range of epidemiological areas. This model presented here could be seen as a simplified version to show single item variation and more complex models might reveal other results.

Thirdly, this analysis is based on the assumption of full compliance to the treatment. The impact of partial compliance on treatment in this population has not been quantified. This study assumed that compliance to the treatment was similar under any strategy, as they all required a 3-day course of treatment. The economic advantage of introducing MFT strategy may be lower for higher on-compliance to either drug in the combination, as this result could affect the acquisition of immunity and reduced effective treatment. Our analysis did not incorporate these effects.

Fourth, the model did not account for neurological sequelae. The chance of these occurring was small, about 2.5 % for under 5 years old and 1.5% for over 5 years old so it would not change the model results significantly.

While all five limitations of the approach should be addressed by future research, ideally by empirically measured parameters, the model presented here provides a means of quantifying the likely range of conditions under which switching to the MFT strategy is likely to be cost-effective. The benefits of MFT strategy will be maximized

when a considerable amount of forward planning and logistical support are in place before advocating switch in policy.

5.4.3 **Conclusion of chapter 5**

In conclusion, changing the first line drug for malaria is a highly complex issue, and a modeling dynamic framework is essential to consider the trade-offs between current and future costs and effects. This study demonstrates that the MFT strategies outperform the single first-line strategies in terms of costs and benefits across the wide range of epidemiological and economic scenarios.

Chapter 6**: Final discussion and conclusion**

6.1 **Discussion about the costs –effectiveness of initiating ART during TBM treatment**

6.1.1 **Main findings**

In order to identify previous published work evaluating costs and quality of life of HIV-infected patients with TBM**, Chapter 2** presented a literature review of cost studies and quality of life studies of patient with HIV/AIDS and TB as measured using the EQ5D questionnaire. This chapter found nine costing studies and four quality of life studies published between 2000 and 2014. HIV-patients co-infected with TB on antiretroviral therapy were likely to incur mean total costs of $946 per person per year. The review found that treatment costs varied considerably, mainly due to differences in population studied, methods, and cost categories included in each study, even in studies conducted in the same country. As for quality of life studies, the results highlighted the importance of stratifying quality of life estimates by disease severity and the use of ART. The review also highlighted significant differences in published of quality of life estimates when studies used different methods and populations to elicit quality of life.

The main findings of **chapter 3** suggested that deferring ART until 2 months after intensive TB treatment proved more cost-effective than early ART (1 week after instigation of TBM treatment) for patients co-infected with TBM and HIV. The overall costs of treating HIV-associated TBM per patient during 9 months of treatment

in Vietnam were substantial and estimated at approximately $2000 at current market value of ARV drugs in 2013. HIV-and TBM co-infection decreased patient's quality of life greatly by 50% and 20% from their healthy life at 2months and 9 months of treatment, respectively.

6.1.2 **Challenges in evaluating the costs –effectiveness of initiating ART during TBM treatment**

These two chapters reflect the challenges for the design, conduct and use of economic evaluation undertaken alongside a randomized clinical trial in a LMIC country. The central challenge for our trial based economic evaluation in Vietnam is the accessibility, and the quality of the data. Cost data contained substantial zeros, and missing values. Two-part regression models, multiple imputation techniques were undertaken to deal with these cost issues. Another issue is the design on the recall period in the questionnaire to collect patient healthcare costs, therefore weekly patient costs had to be derived from the survey. Simple extrapolation was employed to deal with this issue. As for quality of life, there was little evidence of meningitis patients health related quality of life changing from a health state worse than death. Methods such as area under the curve and linear interpolation were adopted to deal with these issues.

6.2 **Discussion about the modelling based economic evaluation of implementing the multiple first-line drugs to treat malaria**

6.2.1 **Main findings:**

A major finding of this part of the thesis was that the changes in national first-line drug policy that all strategies aimed to address artemisinin resistance requiring detailed research to accurately identify the program costs. In **Chapter 4**, a review of the literature identified that only a small portion of studies reporting the costs associated with these changes. The program cost of changing national drugs accounted for a large part of the total costs (40% to 60%) but was often excluded from national studies.

Chapter 5 demonstrated that the MFT strategy was superior to the single first-line therapies in terms of costs and effectiveness across a wide range of resistance rates, treatment coverage and transmission settings over a 20-year time period. The analysis also indicates that the drug price would have to increase 10 to 30-fold for the MFT strategy to be no longer cost-effective compared to the single first-line drugs.

6.2.2 **Challenges in evaluating the economic evaluation of implementing the multiple first-line drugs to treat malaria**

The biggest challenge of populating the economic model of changing single –first line drugs was a lack of evidence on the primary costs of such implementation. Estimates of the drug price of the MFT strategy (including the costs of delivering the drugs) were made, but these required assumptions regarding the structure of the supply chain under the MFT model. To deal with these issues of uncertainties in the data used to inform the model, threshold analysis, univariate and probabilistic sensitivity were undertaken to provide a more accurate representation of the uncertainty around the modeling results.

6.3 Overall challenges in conducting the trial-based economic evaluation and model-based economic evaluations and how these challenges would affect the results and more generally for future economic evaluation work in Vietnam and suggested ways to address this gap:

This part highlights key challenges on 5 methodological areas: i) The lack of cost and resource use data in trial and model-based study ii) The use of DALYs versus QALYS and their limits as outcome measures iii) The challenges of modeling resistance and infectious diseases iv) The value of conducting EVPI or multiple imputation

First, the lack of cost and resource use data of the trial-based study diminishes the accuracy of the cost estimates. Currently, the unit cost and the quantity of resource were not collected in this analysis. A week of waiting from the onset of clinical trial to the start of the economic project increased the missing data. The productivity losses were not fully been quantified in terms of paid and unpaid work. The analysis did not take account of reduced productivity due to unpaid work while a severe disease like HIV-TB meningitis, more than half of these patients performed unpaid work such as housework, care-takers. Methods for adjusting effect and cost data for non-adherence in the non-trial conditions have not been established in this analysis. All these issues above could be due to the use of a non-standardized questionnaire or inefficient record-keeping at the hospital during the period 2005 to 2007 in Vietnam. Future economic evaluations (EE) in Vietnam could consider adopting the “reference case” which was proposed by the Bill and Melinda Gates Foundation [114] in 2013 and 2014 to improve the cost data collection methods and consistency across the EE studies.

Another research gap is the limited collection of detailed cost data that account for changing the national drug policy among countries. Gaps in both data on these costs and technical understanding of the process of change currently prohibit confidence of future model projections. Additionally, the model-based study may not capture all the costs involved in the supply chain ranging from the new drug development to the end-patient. Further investigations should be focused on the service provision aspects of the supply chain or the individual behavior to understand which actors impact decisions that might trigger drug resistance [246,247] . All these issues not only a problem confined to LMICs but has also been documented in many HICs [248].

Second, a notable gap in research is the comprehensive disability metrics such as QALYs or DALYs to capture the disease burden of meningitis infection. The use of QALYs in measuring the neurological disability metrics has not been validated in previous studies. The EQ-5D scores are only available for one Asian country that is Thailand therefore diminishes its usefulness in other settings such as Vietnam. It is difficult to utilize the published findings of quality weights of HIV-TBM patients as often the patients were interviewed only in the first weeks following diagnosis, again after 2 months and 9 months treatment, the report did not cover the utility weight for the whole treatment period. For health conditions associated with meningitis, the use of a specific disease measurement of health status along with the EQ-5D or disability weight could be the optimal choice to provide comprehensive assessment. More research is needed to ascertain how disease burden of meningitis or co-infection evolve and experience of health management of co-infection from various national settings.

Third, the common challenges of modelling resistance and infectious diseases were particularly evident in economic evaluations carried out in the Vietnamese setting. Nearly all the model-based studies used Markov model (90% of the model-based studies or 10% was not clear from the paper [2]). None of studies modelling infectious diseases used the transmission dynamic models as Drake et al (2015) [194] recommended. Our decision economic modelling used simplifying assumption of homogeneous transmission for the population in similar age-group and transmission settings progressing from treatment failures to severe malaria and finally death. However, malaria transmission from treatment failures to severe malaria and either to death or survive can be highly heterogeneous between individuals from different geography. To capture this heterogeneity more accurately, the economic decision model in this analysis should be expanded further to combine different treatment management models and can be built internally within the epidemiological models.

Fourth, it is also important that future economic evaluations incorporate the value of expected value of information or multiple imputation [192,193]. None of the health economics studies in Vietnam employed the calculations of EVPI[2]. In contrast, the EVPIs contain many benefits as economic evaluation always involves a degree of uncertainty. The expected value of perfect information analysis tries to measure the expected cost of that uncertainty. This is the value (in money terms) of removing all uncertainty from such an analysis. Here I have shown that the MFT is a best choice in most cases when EVPI always equal to zero in all decision makers' willingness to

pay values. On the other hand, multiple imputation has been shown to be robust in dealing with high proportion of missing data. However, the pooling results and how the MI incorporated in the construction of acceptability curve was not always intuitive in the literature.

Most of the health economics evaluations in Vietnam used the WHO thresholds that was criticised to be set so high that nearly all new interventions were considered 'cost-effective' and therefore may not contribute effectively to priority setting [1,2]. A study in Vietnam [249] estimated willingness to pay for a QALY gained in Bavi district, Hanoi (the capital of Vietnam) in 2014 ranging from $667.3 – $993.1. These WTP/QALY values were slightly lower than the recommendation of WHO (GDP= $2000 per capita in Vietnam in 2013). Therefore, the authors recommended having more than one threshold for every situation based on the disease severity to provide more accurate country specific thresholds.

Who is the decision maker and target user of this work and how they were involved in the study? How this work was disseminated and present to decision makers in Vietnam?

The treatment costs of the trial based study were disaggregated into two types of costs: hospital health care costs and patient healthcare costs. The findings of the trial-based economic evaluations were aimed for decision makers, patients and their families as well as local healthcare funders such as health insurance. I had presented the proposals and the findings of this trial based economic evaluation at two national health economics conferences in Vietnam in 2012 and 2013, which were held by the

Vietnamese Ministry of Health, and one international conference in Cambodia in 2014. The findings will be published in an international journal to demonstrate that the financial burden of treating HIV/TBM was very high for patients and their caregivers. Cost of ARV and TB medicines and diagnostic tests were important drivers of hospital healthcare costs. Costs for assistance accounted for a major part of direct non-medical costs for HIV-TBM part. The findings of the trial-based economic evaluations will provide the economic evidence for the Health strategy and policy institute which resides within the MoH, that has been tasked to review the existing prices of pharmaceutical and health services packages with the aim to introduce the new Basic Health Service Package by 2018 [247’

The findings of the model-based study can be of a value for a broad variety of health care providers such as public hospitals/ clinics, private and public pharmacies, drug shops and informal outlets. Financing organizations such as the World Bank, the Global Fund and bi-lateral donors provide financing for drug procurement and health system improvement could be interested in the interventions/strategies that delayed antimalarial drug resistance

6.4 **The generalisability of the results and future work**

Although the trial-based economic evaluation was based on some limited sources of information, for example on resource use and some of the cost data collected in weekly form in the trial, the findings concerning differences in hospital healthcare costs and health outcomes had the advantage of being based on a high-quality randomized controlled trial, and are therefore likely to be unbiased. Therefore, the results on costs

and outcomes will be useful to inform decision makers about the cost-effectiveness of commencing ART to treat HIV-associated with TBM patients. Further work is now under way to employ the multivariate model in order to identify the main drivers of the treatment costs, and to analyse the EQ-5D index scores alongside a range of clinical and socio-economic data. The limitations of conducting economic evaluations alongside clinical trials are well-known in LMICs which are the scarcity, quality and accessibility of data [33]. Other challenges include the methodological variation on measurement of costs and health outcomes across economic evaluations; and the majority of studies do not offer sufficient information about currency conversion [250].

In the model-based study, the MFT strategy provided substantial health benefits at cost savings making this strategy attractive and feasible in both high and low transmission settings, and in some scenarios, the MFT strategy can lead to local elimination. Two areas of modeling methodology can be improved further. Firstly, the decision model could be developed by adding realistic features that are known to have important effects on the economics of changing national drug policy, such as the interaction between different models of supply chain of drugs, different implementation strategies, and the impact of socioeconomic factors. Secondly, the decision model can also be developed to incorporate decision makers' prior beliefs and combined with evidence from clinical trials and other information sources in a Bayesian approach [251]. This would generate a set of informed posterior beliefs about the effectiveness of a public health intervention which can then be compared against costs [252].

Vietnam healthcare is a growing industry. The people's expectation for health in Vietnam is becoming high and they now demand better healthcare and latest treatment. However, the adoption of these new technologies tends to be costly which can increase healthcare costs, for example the introduction of GeneXpert MTB/RIF for TB diagnosis and resistance testing can get results within two hours but its price is likely to be 10 times higher than the traditional diagnostic methods [55]. Increasing health care expenditure and the anticipated drop in donor aid can create constraints in providing adequate healthcare in Vietnam.

Vietnam is urgently in need of the economic evaluation as a formal tool to allocate scare healthcare resources efficiently. However, the development and application of economic evaluation in Vietnam may face some challenges. At present, Vietnam does not have willingness-to-pay thresholds, or its own guidelines for conducting economic evaluation. The numbers of economic evaluation studies in Vietnam are low compared with its neighboring countries, for examples Thailand, or China have already developed and implemented economic guidelines to aid pricing and reimbursement decisions [253]. The majority of publications on economic evaluations in Vietnam utilized poor quality of evidence and had deficient reporting standards that would give misleading results [2,3].Health professionals in Vietnam might lack the understanding about the concepts and methods for conducting economic evaluations. In Vietnam, data collection systems for cost and health outcomes may be far from perfect. Limited data collection may lead to undesirable consequences such as reducing confidence in the accuracy of the conclusions drawn from the analysis [254]. Other Asian countries

have also encountered these barriers to the use of economic evaluation in policy-making [253].

To improve the use of economic evaluation in Vietnam, the findings from this thesis emphasize the need for clinical trials to provide location specific data on costs and effects and for region specific quality of life (QoL) values. This data can then be used to develop economic database that allows users to access to reliable information for competing healthcare programs. There is the need for Vietnamese policy makers to be receptive to the methods of economic evaluations and they are sufficiently informed to interpret the findings. There is also the need for the country to have a standardised set of methodological guidelines that will ensure a high quality of evidence used in the evaluations. Another important reformation is to raise public awareness that healthcare resources are constraint, making choices in healthcare is inevitable, and that economic evaluation helps to make choices by identifying the more cost-effective interventions that offer more QALYs for the same amount of resources used. The policy makers may need to be aware that the QALY maximization concept of economic evaluation may not be well-perceived in Asian countries due to social expectation based on the best interest of patients, social institutional barriers and Buddhist philosophy[251].

The findings from this thesis also emphasize the critical role of modelling where data are not readily available which is normally the case in LMICs. The model-based studies makes an important contribution to understand the growth of drug resistance as this is a very complex process, dependent on a wide variety of societal influences that are not well understood and difficult to predict. In Vietnam, there is a very limited model based studies that examined the full economic impact of drug resistance over

the long time [2]. This is because these studies need to conduct an in-depth analysis of variation in cost-effectiveness across different epidemiological and economic zones that normally take a long term and utilise high capacity of computing technology. Finally, it is recommended that for trial or model based studies need to be done in a transparent way to enable the improvement of the quality and usefulness of the evidence.

6.5 **Concluding remarks**

This thesis demonstrates the application of cost-effectiveness analysis to health care interventions in Vietnam. It uses an internationally accepted methodological framework to undertake these cost-effectiveness studies, and applies them in two ways: first, a trial-based evaluation of the different timing of ART for HIV-associated TBM patients, and second a model-based evaluation of three different strategies for controlling malaria while countering *artemisinin* resistance. In both cases the studies were responding to a lack of information on costs and outcomes for these groups of patients and in both cases the results of these analyses are essential to inform decision-makers about the cost-effectiveness of the available therapies. The results are particularly relevant to Vietnam, but are also relevant internationally, especially in the setting of other LMIC countries. Finally, this thesis not only provides evidence on these two disease areas, but demonstrates more generally how the cost-effectiveness framework can guide policy makers by providing evidence that can improve the allocation of scarce health care resources in resource-constrained settings.

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APPENDICES

Appendix 1: **Modified MRC grading for TBM and WHO clinical stage for HIV/AIDS**

Diagnostic criteria for tuberculous meningitis

Classification	Diagnostic criteria
Definite TBM	Clinical meningitis plus acid-fast bacilli seen in the CSF or *M. tuberculosis* cultured from the CSF
Probable TBM	Clinical meningitis plus one of the following criteria: • Radiographic evidence of pulmonary tuberculosis • Acid-fast bacilli seen in sputum or gastric fluid • Evidence of extra-pulmonary tuberculosis • CT or MRI brain scan features consistent with TBM
Possible TBM	Clinical meningitis plus ≥ 2 of the following criteria: • History of previous tuberculosis • Illness duration > 5 days • Glasgow coma score < 15 • Focal neurological signs and≥ 2 of the following criteria: • Yellow CSF • > 50% lymphocytes in the CSF • CSF glucose < 50% blood glucose

Modified MRC grading for tuberculous meningitis

TBM grade	Diagnostic criteria
Grade I	Glasgow coma score 15, no focal neurology
Grade II	Glasgow coma score 11-14 OR Glasgow coma score 15 with focal neurology
Grade III	Glasgow coma score ≤ 10

WHO clinical staging for HIV/AIDS

Clinical Stage 1
Asymptomatic Persistent generalised lymphadenopathy (PGL) Performance scale 1: asymptomatic, normal activity
Clinical Stage 2
Weight loss, <10% of body weight Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) Herpes zoster, within the last 5 years Recurrent upper respiratory tract infections (e.g. bacterial sinusitis) And/or performance scale 2: symptomatic, normal activity.
Clinical stage 3

Weight loss, >10% of body weight Unexplained chronic diarrhoea, > 1 month Unexplained prolonged fever (intermittent or constant), > 1 month Oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis, within the past year. Severe bacterial infections (e.g. pneumonia, pyomyositis) And/or Performance scale 3: bed-ridden, < 50% of the day during the last month
Clinical stage 4
HIV wasting syndrome, as defined by CDC[1] Pneumocystis carinii pneumonia Toxoplasmosis of the brain Cryptosporidiosis with diarrhoea, >1 month Cryptococcosis, extra pulmonary Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes Herpes Simplex Virus (HSV) infection, mucocutaneous >1 month, or visceral any duration Progressive multifocal leukoencephalopathy (PML) Any disseminated endemic mycosis (e.g. histoplasmosis, coccidioidomycosis) Candidiasis of the oesophagus, trachea, bronchi or lungs Atypical mycobacteriosis, disseminated Non-typhoid Salmonella septicaemia Extra-pulmonary tuberculosis Lymphoma Kaposi's sarcoma (KS) HIV encephalopathy, as defined by CDC[2] And/or Performance scale 4: bed-ridden, > 50% of the day during the last month

(Note: Both definitive and presumptive diagnoses are acceptable)

[1] HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month), or chronic weakness and unexplained prolonged fever (>1 month).

[2] HIV encephalopathy: clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.

Appendix 2: **Search terms for costs and cost-effectiveness of HIV/TBM**

Details of key search terms and search databases for costs, and costs-effectiveness stratified by the search engines.

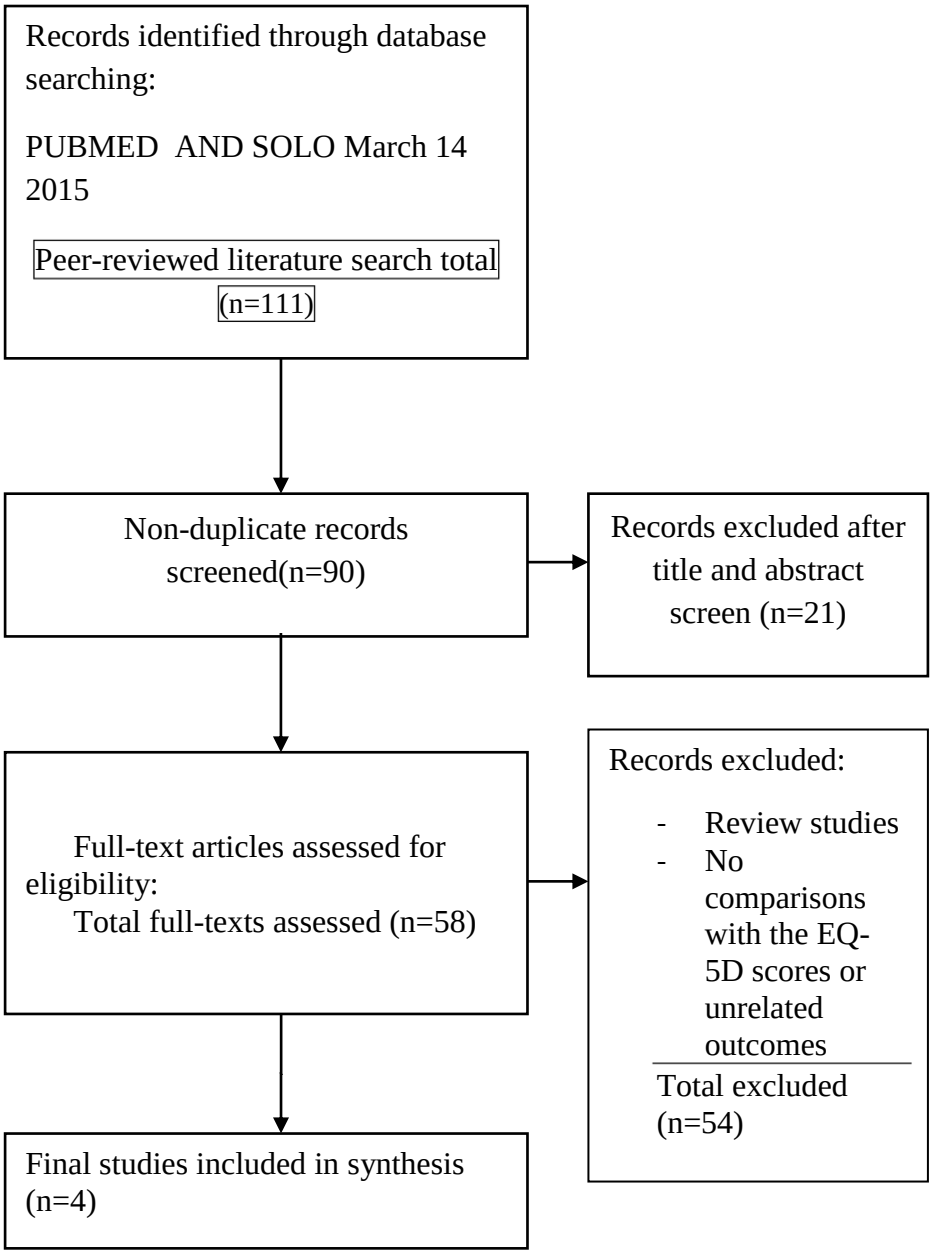
Search topics	Key search terms	Results prompted		
		Pubmed	SSRN	SOLO (Oxford)
Cost	Cost of HIV TB	543	5	353
	Cost of HIV TB in Viet Nam	6	0	3
	Cost of HIV TBM in Viet Nam	0	0	12
	Cost of HIV TBM	0	0	2
	Cost of TBM	21	0	203
	Cost of meningitis	829	2	702
	Cost of meningitis in developing countries	118	0	60
	Cost of HIV meningitis	68	0	35
	Cost of tuberculosis and HIV	387	10	603
Cost-effectiveness of ART	Cost-effectiveness of ART in HIV TBM	0	0	4
	Cost-effectiveness of ART	688	15	100
	Cost-effectiveness of ART timing	4	2	2
	Cost-effectiveness of HIV TB	14	3	115
	Cost-effectiveness of ART in HIV with OIs	26	0	14

Appendix 3**: Search terms for quality of life of HIV/TBM**

Details of key search terms and search databases. This table shows the search keywords for QALYs s stratified by the search engines.

Database	Search terms	Results
PubMed	HIV-TB[All Fields] AND health-related[All Fields] AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) HIV-TB[All Fields] AND EQ-5D[All Fields] ("meningitis"[MeSH Terms] OR "meningitis"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) "Tuberculosis, Meningeal"[Mesh] AND (health-related[All Fields] AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields])) extra[All Fields] AND ("tuberculosis, pulmonary"[MeSH Terms] OR ("tuberculosis"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary tuberculosis"[All Fields] OR ("pulmonary"[All Fields] AND "tuberculosis"[All Fields])) AND EQ-5D[All Fields]	85
SOLO	Menignitis[All Fields] AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND EQ-5D[All Fields] ("meningitis"[MeSH Terms] OR "meningitis"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND EQ-5D[All Fields] ("tuberculosis, meningeal"[MeSH Terms] OR ("tuberculosis"[All Fields] AND "meningeal"[All Fields]) OR "meningeal tuberculosis"[All Fields] OR ("tuberculous"[All Fields] AND "meningitis"[All Fields]) OR "tuberculous meningitis"[All Fields]) AND EQ-5D[All Fields] ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND EQ-5D[All Field	26

Appendix 4**: The flow chart of selecting the studies for health related quality of life studies**



Appendix 5**: The Euroqol EQ-5D questionnaire**

Figure 1: EQ-5D-3L (UK English sample version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

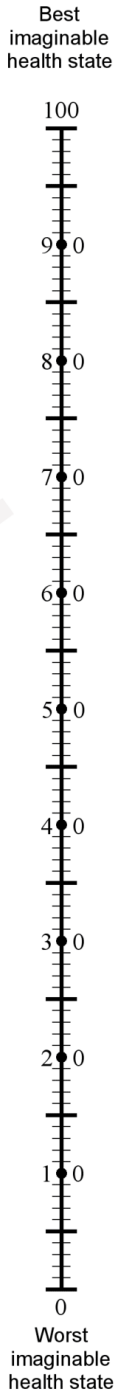
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 6: **The structure of costing questionnaire for HIV/TBM analysis**

Please report the healthcare services which were used during last week (including today's visit at hospital):

1.Did you see the doctors during last week?	1 = No ; 2 = Yes. If yes, please fill in: -Doctor's place (hospital, private clinic) -Total waiting and exam time (hours, minutes) **-Exam cost (1)** -Transport time to the health checkup (hours, minutes) **-Patient's transport cost to the doctor's place (2)** **-Relative's transport cost to accompany the patients to the doctor's place (3)**
2. Did you pay for any medications, fluids, and other health products during last week?	1 = No ; 2 = Yes. If yes, please fill in: -Drug name -Doses and unit cost **-Medication cost (4)**
3. Do you need assistance during last week? - from family members - from friends -from helpers -from nurses -from others	1 = No ; 2 = Yes. If yes, please fill in: -Assistance time per week (hours) **-Assistance cost per week (5)**
4. How much were your **average daily food** expenses during last	**- Patient's food cost (6)** **-Relative's food cost (7)**

week?	
5. Other expenses, excluding above expenses during last week?	**- Other expenses (8)**

Today's health checkup at hospital

1. Please report any transport expenses for today's visit.	-Transport's type -Transport time to today's health checkup (hrs, mins) **-Transport cost (9)**
2. How long do you wait to see the doctor or nurse at the hospital?	-Waiting time (hrs, mins)
3. How long does the health exam take?	-Exam time (hrs, mins)
4. Income lost if not coming today?	1 = No ; 2 = Yes. If yes, please fill in: Type of work if not coming **- Income lost for coming today (10)**
5. Please report any expenses incurred if the caregiver accompanied patients to today's visit.	- Anybody accompanied the patients (Yes/No) - Who accompanied -The time of accompanying (hrs, mins) **- Income lost for accompanying the patient to today's visit (11)** **- Other cost incurred during accompanying (12)**
6. Food expenses and other expenses today?	- Patient's food expenses -Relative's food expenses - Other expenses

Appendix 7: **Inspecting the missing medication costs, and Visual Analogue Scale (VAS)**

This part is divided into 3 parts to assess the types of missing values for the medication costs at 2 months and VAS at 2 months and 9 months.

Firstly, I examined the probability of medication cost at 2 months being missing using the logistic regression, also called a logit model.The output of a logistic regression model using the glm (generalized linear model) function in R is shown as follows:

Call:
glm(formula = is.na(medic) ~ ., family = "binomial", data = dat1)

	Estimate	**Std. Error**	**Pr(>|z|)**
(Intercept)	57.6	42492.9	1.0
Treatment type	3.0	2.6	0.2
Patient's temperature	-0.3	1.0	0.8
TB diagnosis	-20.4	9619.2	1.0
TBMgrade	0.6	1.2	0.6
age	0.0	0.1	0.8
gender	-19.9	15587.9	1.0
hospital	-0.2	1.7	0.9
Treatment days	0.0	0.0	0.4
Hospitalised days	0.0	0.0	0.3
Province	0.9	1.5	0.5
Time for assistance	0.0	0.0	0.5
Time for transport	-32.4	10372.3	1.0
Time for accompanying the patients to hospital visits	0.1	0.1	0.6
Time for accompanying the patients to hospital visits	-0.3	936.4	1.0

Null deviance: 4.8816e+01 on 131 degrees of freedom
Residual deviance: 7.5903e-08 on 115 degrees of freedom
AIC: 34

The logistic regression coefficients refer to the change in the log odds of the outcome for a one-unit increase in the predictor variable. The odds of being missingness are defined as the ratio of the probability of being missing over the

probability of not being missing. The transformation from odds to log of odds is the log transformation because it is difficult to model a variable which has restricted range, such as probability. This transformation converts probability ranging between 0 and 1 to log odds ranging from negative infinity to positive infinity for easier inteptertation. The output shows that none of the variables was statically significant (p >0.5). From this result, I concluded that the probability of medication costs being missing at 2 months did not relate to any other factors. Therefore, the missingness in medication costs at 2 months was likely to follow the MCAR pattern. Therefore complete-cases and multiple imputation were applied to deal with the missing values here.

Secondly, I examined the probability of Visual Analogue Scale (VAS) being missing at 2 months using the logistic regression. Repeat the steps above. The output of a Bayesian logistic regression model using the bayesglm (generalized linear model) function in R is shown as follows:

	Estimate	**Std. Error**	**Pr(>|z|)**
(Intercept)	-9.44	27.73	0.73
type	0.50	1.11	0.65
TB diagnosis	-0.01	1.28	0.99
TBMgrade	1.51	0.95	0.11
age	-0.19	0.12	0.10
gender	1.67	1.34	0.21
hospital	-0.84	1.27	0.51
Treatment days	-0.01	0.01	0.18
Hospitalised days	0.00	0.01	0.92
province	-1.12	1.64	0.49
Time for assistance	0.00	0.01	0.54
Time for transport	-0.14	0.98	0.89
Time for accompanying the patients to hospital visits	-0.09	0.06	0.12
Time for accompanying the patients to hospital visits	-0.01	0.12	0.91

Null deviance: 48.816 on 131 degrees of freedom
Residual deviance: 13.887 on 115 degrees of freedom
AIC: 47.887

Based on these findings, this analysis found no statistically significant variables. The probability of Visual Analogue Scale (VAS) being missing at 2 months did not relate to any other factors. Therefore, the missing values in Visual Analogue Scale (VAS) at 2 months were likely to follow the MCAR pattern. Therefore complete-cases and multiple imputation were applied to deal with these missing values here.

Thirdly, I examined the probability of Visual Analogue Scale (VAS) being missing at 9 months using the logistic regression. Repeat the steps above, the output of a Bayesian logistic regression model using the bayesglm (generalized linear model) function in R is shown as follows:

	Estimate	**Std. Error**	**Pr(>|z|)**
(Intercept)	-11.42	56.97	0.84
type	0.02	1.76	0.99
TB diagnosis	-1.00	1.62	0.54
TBMgrade	1.11	1.24	0.37
age	-0.04	0.15	0.76
gender	-0.62	1.94	0.75
hospital	-0.36	1.64	0.83
Treatment days	0.03	0.15	0.83
Hospitalised days	0.00	0.01	0.83
province	-0.52	1.94	0.79
Time for assistance	0.00	0.01	0.95
Time for transport	-0.24	0.57	0.67
Time for accompanying the patients to hospital visits	0.04	0.08	0.68
Time for accompanying the patients to hospital visits	-0.23	0.13	0.08

Null deviance: 18.4972 on 75 degrees of freedom
Residual deviance: 5.0258 on 59 degrees of freedom
AIC: 39.026

Based on these findings, this analysis found no statistically significant variables. The probability of Visual Analogue Scale (VAS) at 9 months being missing did not relate to any other factors. Therefore, the missing values in Visual Analogue Scale (VAS) at 9 months were likely to follow the MCAR pattern. Complete-cases and multiple imputation were applied here.

Appendix 8: **Analysis of patient health-care cost data with substantial zeros using the two-part models**

The two part models were applied for weekly patient healthcare costs that contained substantial zeros at 2 months, 6 months, 9 months for complete-cases and imputation analysis.

2 months (complete-cases analysis)

Examcost (Complete cases – 2 months)	**Probability of healthcare costs (Logitstic model)**		**Examcost (Complete cases – 2 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	0.04747	0.95492	Treatment type	1.753e-02	0.41230
Examination Time	0.09355	0.00386**	TBM grade	-0.3005	0.00720**
			Hospital	0.3084	0.00548**
			CD4 count	-4.35e-04	0.02433*
Constant	-3.55544	0.01082*	Constant	9.879	1.32e-05***
AIC	52		AIC	105	
*** p<0.001, ** p<0.01, * p<0.05					

Accomcost (Complete cases – 2 months)	**Probability of healthcare costs (Logitstic model)**		**Accomcost (Complete cases – 2 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.821e+01	0.996	Treatment type	-0.0613079	0.807682
Age	2.573e-01	0.250	Age	-0.0364561	0.045165*
Hospital	-1.777e+00	0.314	Hospital	0.0941316	0.695703
Weight	2.226e-02	0.811	Weight	0.0041741	0.790853
Temperature	-1.436e+00	0.232	Temperature	-0.2883314	0.063712
Hospitalised days	3.087e-04	0.969	Hospitalised days	-0.0014554	0.354691
CD4 count	-2.758e-03	0.406	CD4 count	-0.0021859	0.018062*
Constant	8.949e+01	0.990	Constant	23.2603570	1.25e-4***
AIC	35		AIC	2952	
*** p<0.001, ** p<0.01, * p<0.05					

Transportcost (Complete cases – 2 months)	**Probability of healthcare costs (Logitstic model)**		**Transportcost (Complete cases – 2 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	2.126e+14	<2e-16***	Treatment type	5.160e-03	0.9853
Carer's costs accompanying patients	-1.490e+09	<2e-16***	Carer's costs accompanying patients	6.945e-06	2.41e-5***
Income lost	-4.996e+09	<2e-16***	Income lost	-7.949e-06	0.0116*
medic	8.215e+08	<2e-16***	medic	-1.198e-07	0.6866
Examination Time	2.900e+14	<2e-16***	Examination Time	-5.247e-03	0.6271
Carer's time accompanying patients	3.398e+13	<2e-16***	Carer's time accompanying patients	1.929e-02	0.2791
Constant	-1.354e+15	<2e-16***	Constant	1.012e+01	3.53e-16***
AIC	734		AIC	739	
*** p<0.001, ** p<0.01, * p<0.05					

Income lost (Complete cases – 2 months)	**Probability of healthcare costs (Logitstic model)**		**Incomelost (Complete cases – 2 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	4.942e-01	0.1936	Treatment type	-9.876e-03	0.94760
Carer's costs accompanying patients	1.226e-06	0.4985	Carer's costs accompanying patients	5.442e-07	0.34112
Food expenses	-4.507e-07	0.9349	Food expenses	7.559e-06	0.00212**
Constant	-1.517e+00	0.0388*	Constant	1.041e+01	<2e-16***
AIC	174		AIC	998	
*** p<0.001, ** p<0.01, * p<0.05					

Assistant (Complete cases – 2 months)	**Probability of healthcare costs (Logitstic model)**		**Assistant (Complete cases – 2 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.358857	0.445314	Treatment type	-0.339950	0.0249*
TB diagnosis	-0.899191	0.030709*	TB diagnosis	0.157895	0.3422
Weight	-0.120128	0.000194***	Weight	0.004097	0.6850
Hospitalised days	-0.001377	0.633930	Hospitalised days	0.002434	0.0258*
GCS	-0.192999	0.015031*	GCS	0.043168	0.0718
Constant	9.683960	1.79e-05***	Constant	12.738845	<2e-16***
AIC	158		AIC	1461	
*** p<0.001, ** p<0.01, * p<0.05					

Medication (Complete cases – 2 months)	**Probability of healthcare costs (Logitstic model)**		**Medication (Complete cases – 2 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-8.470e-01	0.3830	Treatment type	7.187e+00	0.0573
Hospital	-4.045e+00	0.1418	Hospital	5.076e+02	0.0476*
Other expenses	8.009e-06	0.0234*	Other expenses	-4.317e-04	0.0481*
Age	-1.435e-01	0.1884	Age	-5.953e-01	0.0596
Constant	6.785e+00	0.1128	Constant	-4.898e+02	0.0490*
AIC	42		AIC	143	
*** p<0.001, ** p<0.01, * p<0.05					

Other expenses (Complete cases – 2 months)	**Probability of healthcare costs (Logitstic model)**		**Other expenses (Complete cases – 2 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.5149	0.32726	Treatment type	-0.4036	0.2270
TBM grade	0.9910	0.00842**	TBM grade	-0.3399	0.2197
Gender	1.714	0.03855*	Gender	-3.111e-03	0.9953
Carer's cost assisting the patients	3.007e-06	5.81e-6***	Carer's cost assisting the patients	4.487e-08	0.8989
Treatment days	-6.955e-03	0.03958*	Treatment days	1.298e-03	0.4914
Transport cost	-1.788e-05	0.12994	Transport cost	3.559e-05	0.0208*
Income lost	-3.609e-07	0.95384	Income lost	-9.331e-07	0.7798
Medication	-3.993e-01	0.46195	Medication	0.1894e	0.6306
Constant	-2.884	0.09062	Constant	11.93	3.77e-11***
AIC	114		AIC	853	
*** p<0.001, ** p<0.01, * p<0.05					

Examcost (Complete cases – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Examcost (Complete cases – 6 months)**	**Costs (GLM model)**	
	Coeff	P values		Coeff	P values

	(Log odds)			(VND)	
Treatment type	-0.17463	0.867	Treatment type	1.609	2.57e-15***
Examination Time	-0.15134	0.116	TBM grade	1.609	2.97e-15***
Constant	-1.69563	0.323	Constant	5.075	2.16e-15***
AIC	34		AIC	-58	
*** p<0.001, ** p<0.01, * p<0.05					

Accomcost (Complete cases – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Accomcost (Complete cases – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	3.437e+01	0.999	Treatment type	-1.870e-01	0.444
Hospitalised days	-2.224e-02	1.000	Hospitalised days	-8.173e-04	0.530
Carer's time accompanying patients	3.661e+01	0.995	Carer's time accompanying patients	6.221e-02	2.35e-07***
Income lost	-1.943e-03	0.997	Income lost	-1.426e-06	0.674
Constant	-8.503e+01	0.999	Constant	1.056e+01	<2e-16***
AIC	10		AIC	1965	
*** p<0.001, ** p<0.01, * p<0.05					

Transportcost (Complete cases – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Transportcost (Complete cases – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.044e-01	0.92134	Treatment type	2.029e-02	0.9501
Carer's costs accompanying patients	1.124e-05	0.49499	Carer's costs accompanying patients	5.660e-06	0.0135*
Income lost	4.767e-05	0.30084	Income lost	8.121e-06	0.1451
medic	1.869e-03	0.99707	medic	2.396e-06	0.3159
Examination Time	5.672e-01	0.00175**	Examination Time	2.996e-03	0.8533
Carer's time accompanying patients	-1.279e-02	0.83899	Carer's time accompanying patients	3.739e-02	0.0811
Constant	-1.502e+00	0.43101	Constant	1.010e+01	<2e-16***
AIC	43		AIC	1949	
*** p<0.001, ** p<0.01, * p<0.05					

Income lost (Complete cases – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Income lost (Complete cases – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-4.466e-01	0.343	Treatment type	-2.097e-01	0.341
Carer's costs accompanying patients	-5.230e-07	0.874	Carer's costs accompanying patients	5.593e-07	0.825
Food expenses	-6.931e-06	0.407	Food expenses	3.974e-06	0.326
Constant	2.560e-01	0.782	Constant	1.084e+01	<2e-16***
AIC	118		AIC	622	
*** p<0.001, ** p<0.01, * p<0.05					

Assistant (Complete cases – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Assistant (Complete cases – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.978889	0.02759*	Treatment type	-0.407518	0.182
TB diagnosis	-1.048225	0.07573	TB diagnosis	0.306841	0.382

Weight	-0.089089	0.03640*	Weight	-0.006459	0.700
Hospitalised days	0.007213	0.13346	Hospitalised days	0.002335	0.220
GCS	-0.162426	0.08560	GCS	-0.014252	0.720
Constant	8.528786	0.00443**	Constant	13.742760	3.45e-10***
AIC	101		AIC	722	
*** p<0.001, ** p<0.01, * p<0.05					

Medication (Complete cases – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Medication (Complete cases – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	1.1633088	0.34660	Treatment type	2.446e+00	0.243
Examination cost	0.0001987	0.03095*	Examination cost	1.067e-04	0.274
Carer's time accompanying patients	0.1650286	0.06424			
Constant	-8.4407859	0.00553**	Constant	6.254e+00	0.169
AIC	31		AIC	100	
*** p<0.001, ** p<0.01, * p<0.05					

Other expenses (Complete cases – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Other expenses (Complete cases – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.837e-01	0.828461	Treatment type	-3.022e-01	0.769
TBM grade	-4.711e-02	0.939571	TBM grade	4.081e-01	0.547
Gender	-6.722e-01	0.668235	Gender	-6.259e-01	0.733
Carer's cost assisting the patients	4.144e-06	0.000377***	Carer's cost assisting the patients	-3.996e-07	0.802
Treatment days	-1.472e-02	0.247405	Treatment days	2.342e-04	0.989
Transport cost	-5.549e-06	0.315691	Transport cost	-3.216e-06	0.726
Income lost	4.610e-06	0.791267	Income lost	-2.338e-05	0.709
Medication	1.651e-01	0.841344	Medication	1.097e+00	0.408
Constant	1.798e+00	0.677393	Constant	1.006e+01	0.153
AIC	64		AIC	349	
*** p<0.001, ** p<0.01, * p<0.05					

Accomcost (Complete cases – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Accomcost (Complete cases – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	0.02542	0.922	Treatment type	-1.0986	0.19711
Carer's time accompanying patients	0.07359	8.05e-07***			
Constant	9.98515	<2e-16***	Constant	3.9318	0.00974**
AIC	1650		AIC	53	
*** p<0.001, ** p<0.01, * p<0.05					

Transportcost (Complete cases – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Transportcost (Complete cases – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	0.8666	0.44168	Treatment type	-0.19651	0.718
Examination Time	0.3646	0.00338**	Examination Time	0.01181	0.632
Constant	-1.9008	0.30147	Constant	11.91983	<2e-16***
AIC	28		AIC	1786	
*** p<0.001, ** p<0.01, * p<0.05					

Income lost (Complete cases – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Income lost (Complete cases – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.12835	0.04681*	Treatment type	-0.13792	0.19299
TBM grade	-0.07421	0.85727	TBM grade	-0.26514	0.00200**
Temperature	-0.39392	0.25966	Temperature	0.17194	0.00809**
Job	-0.36577	0.01755*	Job	0.01283	0.68878
Medication	1.64457	0.00676**	Medication	-0.25236	0.03657*
Constant	14.43379	0.26462	Constant	5.39470	0.02257*
AIC	96		AIC	661	
*** p<0.001, ** p<0.01, * p<0.05					

Assistant (Complete cases – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Assistant (Complete cases – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.42256	0.6316	Treatment type	-1.353e-01	0.38238
Hospital	-2.48089	0.0253*	Food expenses	-2.887e-06	0.25889
Age	0.11430	0.1200	Other expenses	-7.125e-06	0.08722
Previous TB	-2.71631	0.0168*	Carer's costs accompanying patients	-1.891e-06	0.22428
Temperature	0.56085	0.3704	Income lost	1.891e-05	0.05722
			Province	-1.440e+00	0.00527**
GCS	-0.14852	0.3667			
Constant	-11.99269	0.6023	Constant	1.565e+01	4.3e-05***
AIC	61		AIC	286	
*** p<0.001, ** p<0.01, * p<0.05					

Medication (Complete cases – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Medication (Complete cases – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-2.035e+01	0.996	Treatment type	NA	NA
Food expenses	1.684e-05	0.335	Food expenses	1.514e-05	NA
Other expenses	1.090e-04	0.145	Other expenses	NA	NA
Constant	1.535e+01	0.997	Constant	1.104e+01	NA
AIC	18		AIC	NaN	
*** p<0.001, ** p<0.01, * p<0.05					

Other expenses (Complete cases – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Other expenses (Complete cases – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	0.2778	0.77995	Treatment type	-1.0986	0.0823
Medication	-1.0026	0.32745	Medication	1.9051	0.0629
Carer's cost assisting the patients	-2.7909	0.00505**	Carer's cost assisting the patients	0.1823	0.4231
status9mo	0.4998	0.70640	status9mo	-0.5108	0.1736
Constant	2.6570	0.33331	Constant	9.6487	0.0286*
AIC	41		AIC	113	
*** p<0.001, ** p<0.01, * p<0.05					

Examcost	**Probability of healthcare**		**Examcost**	**Costs (GLM model)**	

(Imputation – 2 months)	costs (Logitstic model)		(Imputation – 2 months)		
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	0.04747	0.95492	Treatment type	1.753e-02	0.41230
Examination time	0.09355	0.00386**	TBM grade	-3.005e-01	0.00720**
			Hospital	3.084e-01	0.00548**
			cd4count	-4.353e-04	0.02433*
Constant	-3.55544	0.01082*	Constant	9.879e+00	1.32e-05***
AIC	52		AIC	105	
*** p<0.001, ** p<0.01, * p<0.05					

Accomcost (Imputation – 2 months)	Probability of healthcare costs (Logitstic model)		Accomcost (Imputation – 2 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.815e+01	0.996	Treatment type	0.0189047	0.937087
Age	2.613e-01	0.253	Age	-0.0388234	0.023237*
Hospital	-1.626e+00	0.346	Hospital	0.1917349	0.399864
Weight	1.555e-02	0.866	Weight	0.0043658	0.772223
Temperature	-1.356e+00	0.250	Temperature	-0.2487932	0.089937
Hospitalised days	1.807e-04	0.982	Hospitalised days	-0.0017943	0.219454
cd4count	-2.774e-03	0.401	cd4count	-0.0021599	0.017035*
Constant	8.635e+01	0.990	Constant	21.5934831	0.000162***
AIC	35		AIC	3097	
*** p<0.001, ** p<0.01, * p<0.05					

Transportcost (Imputation – 2 months)	Probability of healthcare costs (Logitstic model)		Transportcost (Imputation – 2 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	7.576e+01	1	Treatment type	-8.602e-01	1
Carer's costs accompanying patients	4.368e-04	1	Carer's costs accompanying patients	3.739e-06	1
Income lost	9.816e-04	1			
medic	2.062e-05	1			
Examination time	2.970e+00	1			
Carer's time accompanying patients	-5.672e+00	1			
Constant	-9.769e+01	1	Constant	1.087e+01	NA
AIC	43		AIC	NaN	
*** p<0.001, ** p<0.01, * p<0.05					

Income lost (Imputation – 2 months)	Probability of healthcare costs (Logitstic model)		Income lost (Imputation – 2 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	4.942e-01	0.1936	Treatment type	-9.876e-03	0.94760
Carer's costs accompanying patients	1.226e-06	0.4985	Carer's costs accompanying patients	5.442e-07	0.34112
Food expenses	-4.507e-07	0.9349	Food expenses	7.559e-06	0.00212**
Constant	-1.517e+00	0.0388*	Constant	1.041e+01	<2e-16***
AIC	169		AIC	1021	
*** p<0.001, ** p<0.01, * p<0.05					

Assistance cost	Probability of healthcare	Assistant	Costs (GLM model)

(Imputation – 2 months)	costs (Logitstic model)		(Imputation – 2 months)		
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.358857	0.445314	Treatment type	-0.339950	0.0249*
TB diagnosis	-0.899191	0.030709*	TB diagnosis	0.157895	0.3422
Weight	-0.120128	0.000194***	Weight	0.004097	0.6850
Hospitalised days	-0.001377	0.633930	Hospitalised days	0.002434	0.0258*
GCS	-0.192999	0.015031*	GCS	0.043168	0.0718
Constant	9.683960	1.79e-05***	Constant	12.738845	<2e-16***
AIC	158		AIC	1461	
*** p<0.001, ** p<0.01, * p<0.05					

Medication (Imputation – 2 months)	Probability of healthcare costs (Logitstic model)		Medication (Imputation – 2 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.633e-08	1	Treatment type	-1.457e+00	0.6330
Hospital	-1.259e-08	1	Hospital	-1.183e+00	0.7483
Other expenses	-9.805e-13	1	Other expenses	3.421e-06	0.5425
Age	2.060e-09	1	Age	-7.239e-02	0.8480
Constant	2.457e+01	1	Constant	1.715e+01	0.0765
AIC	10		AIC	241	
*** p<0.001, ** p<0.01, * p<0.05					

Other expenses (Imputation – 2 months)	Probability of healthcare costs (Logitstic model)		Other expenses (Imputation – 2 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.5149	0.32726	Treatment type	-0.4036	0.2270
TBM grade	0.9910	0.00842**	TBM grade	-0.3399	0.2197
Gender	1.714	0.03855*	Gender	-3.111e-03	0.9953
Carer's cost assisting the patients	3.007e-06	5.81e-6***	Carer's cost assisting the patients	4.487e-08	0.8989
Treatment days	-6.955e-03	0.03958*	Treatment days	1.298e-03	0.4914
Transport cost	-1.788e-05	0.12994	Transport cost	3.559e-05	0.0208*
Income lost	-3.609e-07	0.95384	Income lost	-9.331e-07	0.7798
Medication	-3.993e-01	0.46195	Medication	0.1894e	0.6306
Constant	-2.884	0.09062	Constant	11.93	3.77e-11***
AIC	114		AIC	853	
*** p<0.001, ** p<0.01, * p<0.05					

Exam cost (Imputation – 6 months)	Probability of healthcare costs (Logitstic model)		Examcost (Imputation – 6 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.17463	0.867	Treatment type	1.609	2.57e-15***
Examination time	-0.15134	0.116	TBM grade	1.609	2.97e-15***
Constant	-1.69563	0.323	Constant	5.075	2.16e-15***
AIC	34		AIC	-58	
*** p<0.001, ** p<0.01, * p<0.05					

Accomcost (Imputation – 6 months)	Probability of healthcare costs (Logitstic model)		Accomcost (Imputation – 6 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	3.437e+01	0.999	Treatment type	-1.870e-01	0.444
Hospitalised days	-2.224e-02	1.000	Hospitalised days	-8.173e-04	0.530
Carer's time	3.661e+01	0.995	Carer's time	6.221e-02	2.35e-07***

accompanying patients			accompanying patients		
Income lost	-1.943e-03	0.997	Income lost	-1.426e-06	0.674
Constant	-8.503e+01	0.999	Constant	1.056e+01	<2e-16***
AIC	10		AIC	1965	
*** p<0.001, ** p<0.01, * p<0.05					

Transport cost (Imputation – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Transportcost (Imputation – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.044e-01	0.92134	Treatment type	2.029e-02	0.9501
Carer's costs accompanying patients	1.124e-05	0.49499	Carer's costs accompanying patients	5.660e-06	0.0135*
Income lost	4.767e-05	0.30084	Income lost	8.121e-06	0.1451
medic	1.869e-03	0.99707	medic	2.396e-06	0.3159
Examination time	5.672e-01	0.00175**	Examination time	2.996e-03	0.8533
Carer's time accompanying patients	-1.279e-02	0.83899	Carer's time accompanying patients	3.739e-02	0.0811
Constant	-1.502e+00	0.43101	Constant	1.010e+01	<2e-16***
AIC	43		AIC	1949	
*** p<0.001, ** p<0.01, * p<0.05					

Income lost (Imputation – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Income lost (Imputation – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-5.075e-01	0.3157	Treatment type	-5.050e-02	0.847
grade4	-5.981e-02	0.9070	grade4	-5.849e-02	0.830
disability.base	3.890e-01	0.5341	disability.base	-4.533e-01	0.385
anemia	-1.217e+00	0.0248*	anemia	2.461e-01	0.349
Carer's costs accompanying patients	-7.638e-07	0.8262	Carer's costs accompanying patients	1.200e-06	0.656
Food expenses	-4.623e-06	0.5907	Food expenses	-6.893e-07	0.926
Constant	1.326e+00	0.5669	Constant	1.183e+01	7.34e-06***
AIC	119		AIC	622	
*** p<0.001, ** p<0.01, * p<0.05					

Assistant (Imputation – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Assistant (Imputation – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.978889	0.02759*	Treatment type	-0.407518	0.182
TB diagnosis	-1.048225	0.07573	TB diagnosis	0.306841	0.382
Weight	-0.089089	0.03640*	Weight	-0.006459	0.700
Hospitalised days	0.007213	0.13346	Hospitalised days	0.002335	0.220
GCS	-0.162426	0.08560	GCS	-0.014252	0.720
Constant	8.528786	0.00443**	Constant	13.742760	3.45e-10***
AIC	101		AIC	722	
*** p<0.001, ** p<0.01, * p<0.05					

Medication (Imputation – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Medication (Imputation – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values

Treatment type	1.1633088	0.34660	Treatment type	2.446e+00	0.243
Examination cost	0.0001987	0.03095*	Examination cost	1.067e-04	0.274
Carer's time accompanying patients	0.1650286	0.06424			
Constant	-8.4407859	0.00553**	Constant	6.254e+00	0.169
AIC	31		AIC	100	
*** p<0.001, ** p<0.01, * p<0.05					

Other expenses (Imputation – 6 months)	**Probability of healthcare costs (Logitstic model)**		**Other expenses (Imputation – 6 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.837e-01	0.828461	Treatment type	-3.022e-01	0.769
TBM grade	-4.711e-02	0.939571	TBM grade	4.081e-01	0.547
Gender	-6.722e-01	0.668235	Gender	-6.259e-01	0.733
Carer's cost assisting the patients	4.144e-06	0.000377***	Carer's cost assisting the patients	-3.996e-07	0.802
Treatment days	-1.472e-02	0.247405	Treatment days	2.342e-04	0.989
Transport cost	-5.549e-06	0.315691	Transport cost	-3.216e-06	0.726
Income lost	4.610e-06	0.791267	Income lost	-2.338e-05	0.709
Medication	1.651e-01	0.841344	Medication	1.097e+00	0.408
Constant	1.798e+00	0.677393	Constant	1.006e+01	0.153
AIC	64		AIC	349	
*** p<0.001, ** p<0.01, * p<0.05					

Accomcost (Imputation – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Accomcost (Imputation – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-1.0986	0.19711	Treatment type	0.02542	0.922
			Carer's time accompanying patients	0.07359	8.05e-07***
Constant	3.9318	0.00974**	Constant	9.98515	<2e-16***
AIC	53		AIC	1650	
*** p<0.001, ** p<0.01, * p<0.05					

Transportcost (Imputation – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Transportcost (Imputation – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	0.8666	0.44168	Treatment type	-0.19651	0.718
Examination time	0.3646	0.00338**	Examination time	0.01181	0.632
Constant	-1.9008	0.30147	Constant	11.91983	<2e-16***
AIC	28		AIC	1786	
*** p<0.001, ** p<0.01, * p<0.05					

Income lost (Imputation – 9 months)	**Probability of healthcare costs (Logitstic model)**		**Income lost (Imputation – 9 months)**	**Costs (GLM model)**	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.8453	0.10441	Treatment type	-0.14033	0.17582
TBM grade	-0.2284	0.55418	TBM grade	-0.26779	0.00139**
Temperature	-0.2936	0.38196	Temperature	0.16982	0.00737**
Medication	1.5114	0.00757**	Medication	-0.24931	0.03490*
Constant	9.9270	0.42319	Constant	5.49767	0.01733*
AIC	101		AIC	661	

*** p<0.001, ** p<0.01, * p<0.05

Assistant (Imputation – 9 months)	Probability of healthcare costs (Logitstic model)		Assistant (Imputation – 9 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-0.42256	0.6316	Treatment type	3.114e-01	0.362
Hospital	-2.48089	0.0253*	Food expenses	-4.096e-06	0.502
Age	0.11430	0.1200	Other expenses	1.456e-06	0.842
Skin	-2.10903	0.0583	Transport cost	-7.465e-07	0.119
Previous TB	-2.71631	0.0168*	Carer's costs accompanying patients	1.063e-06	0.756
Temperature	0.56085	0.3704	Income lost	3.386e-05	0.101
grade4	-1.33508	0.1300			
Oral	1.08446	0.3048			
GCS	-0.14852	0.3667			
Constant	-11.99269	0.6023	Constant	1.327e+01	3.4e-05***
AIC	61		AIC	314	

*** p<0.001, ** p<0.01, * p<0.05

Medication (Imputation – 9 months)	Probability of healthcare costs (Logitstic model)		Medication (Imputation – 9 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	-6.693e-01	0.3571	Treatment type	-4.145e-12	0.8
Food expenses	-1.513e-05	0.2441	Food expenses	7.798e-09	0.7
Other expenses	1.169e-04	0.0201*	Other expenses	3.2e-09	1
Constant	-1.994e-01	0.8945	Constant	1.800e+05	1
AIC	57		AIC	3	

* This result is from bayesglm() function in R

*** p<0.001, ** p<0.01, * p<0.05

Other expenses (Imputation – 9 months)	Probability of healthcare costs (Logitstic model)		Other expenses (Imputation – 9 months)	Costs (GLM model)	
	Coeff (Log odds)	P values		Coeff (VND)	P values
Treatment type	0.2778	0.77995	Treatment type	-1.0986	0.0823
Medication	-1.0026	0.32745	Medication	1.9051	0.0629
Carer's cost assisting the patients	-2.7909	0.00505**	Carer's cost assisting the patients	0.1823	0.4231
status9mo	0.4998	0.70640	status9mo	-0.5108	0.1736
Constant	2.6570	0.33331	Constant	9.6487	0.0286*
AIC	41		AIC	113	

*** p<0.001, ** p<0.01, * p<0.05

Appendix 9**: Patient's types of work at baseline, 2 months, 6 months, 9 months**

	BASELINE				**2 MONTHS**				**6 MONTHS**				**9 MONTHS**			
Work Without come	Immediate ART	Deferred ART	Total	p-values	Immediate ART	Deferred ART	Total	p-values	Immediate ART	Deferred ART	Total	p-values	Immediate ART	Deferred ART	Total	p-values
Doing nothing	17 (61%)	11 (39%)	28		20 (44%)	26 (56%)	46		19 (53%)	17 (47%)	36		11 (37%)	19 (63%)	30	
Housework	27 (53%)	24 (47%)	51		20 (46%)	23 (53%)	43		15 (38%)	24 (62%)	39		3 (60%)	2 (40%)	5	
Employment	9 (35%)	17 (65%)	26		1 (25%)	3 (75%)	4		3 (75%)	1 (25%)	4		1 (100%)	0 (0%)	1	
Others	47 (48%)	52 (53%)	99	**0.25**	20 (51%)	19 (49%)	39	**0.74**	8 (57%)	6 (43%)	14	**0.37**	7 (47%)	8 (53%)	15	**0.47**
Missing values									0	1 (100%)	1		14 (56%)	11 (44%)	25	
Column Total	100 (49%)	104 (51%)	204		61 (46%)	71 (54%)	132		45 (48%)	49 (52%)	94		36 (47%)	40 (53%)	76	

p-values from Chi-square tests

Appendix 10: **The average societal costs and the differences in societal costs per participant for different sub-groups over the duration of the trial (up to 9 months)**

The results represent the KMSA imputation analysis (Year 2013 Currency: US dollars, 1USD = 22,000VND**)**

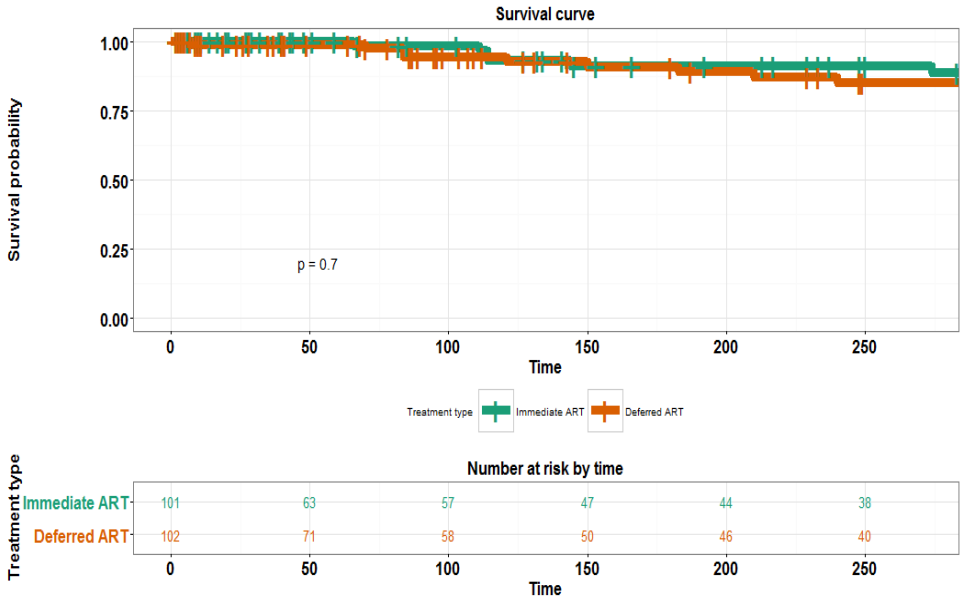
Societal costs (imputation-KMSA)	**Immediate ART (n =101)**		**Deferred ART (n =103)**		**Differences in costs (Immediate ART – deferred ART)**
	Mean	**N**	**Mean**	**N**	**Mean (99%CIs)**
CD4 counts ≥50 cells/mm3	4730 (4064)	42	3919 (2981)	46	811 (-538 2084)
CD4 counts ≤50 cells/mm3	3631 (3166)	54	3545 (2993)	52	86 (-986 1222)
Ho Chi Minh city	4001 (3672)	79	3465 (2957)	85	536 (-387 1500)
Other provinces	4219 (3253)	22	5078 (2866)	18	-859 (-2771 918)
TBM grade_1	5162 (2930)	32	4509 (2418)	35	653 (-560 1801)
TBM grade _2	4542 (4154)	40	3900 (3102)	40	642 (-786 2067)
TBM grade _3	2138 (2589)	28	2555 (3186)	28	-417 (-1757 1074)
2 months survival times	1390 (1406)	61	1080 (1123)	71	310 (-105 713)
6 months survival times	7387 (5518)	45	5804 (1281)	49	1583 (-828 4294)
9 months survival times	7349 (995)	36	6785 (1010)	40	564 (182 994)

Appendix 11: **The average QALYs and the differences in QALYs per participant for different sub-groups over the duration of the trial (up to 9 months)**

The results represent the KMSA-imputation analysis

Societal costs (imputation-KMSA)	Immediate ART (n =101)		Deferred ART (n =103)		Differences in costs (Immediate ART – deferred ART)
	Mean (SD)	N	Mean (SD)	N	Mean (99%CIs)
CD4 counts ≥50 cells/mm3	0.2 (0.28)	42	0.27 (0.28)	46	-0.07 (-0.16 0.02)
CD4 counts ≤50 cells/mm3	0.15 (0.24)	54	0.14 (0.25)	52	0.01 (-0.06 0.08)
Ho Chi Minh city	0.16 (0.25)	79	0.18 (0.28)	85	-0.02 (-0.09 0.04)
Other provinces	0.18 (0.27)	22	0.32 (0.24)	18	-0.15 (-0.28 -0.03)
TBM grade_1	0.28 (0.28)	32	0.3 (0.28)	34	-0.02 (-0.12 0.09)
TBM grade _2	0.14 (0.27)	40	0.21 (0.27)	40	-0.07 (-0.16 0.02)
TBM grade _3	0.06 (0.12)	28	0.07 (0.22)	28	-0.01 (-0.08 0.07)
2 months survival times	0.02 (0.06)	61	0.02 (0.05)	71	0.01 (-0.01 0.02)
6 months survival times	0.12 (0.17)	45	0.13 (0.17)	49	0 (-0.12 0.11)
9 months survival times	0.39 (0.29)	36	0.47 (0.25)	40	-0.07 (-0.17 0.02)

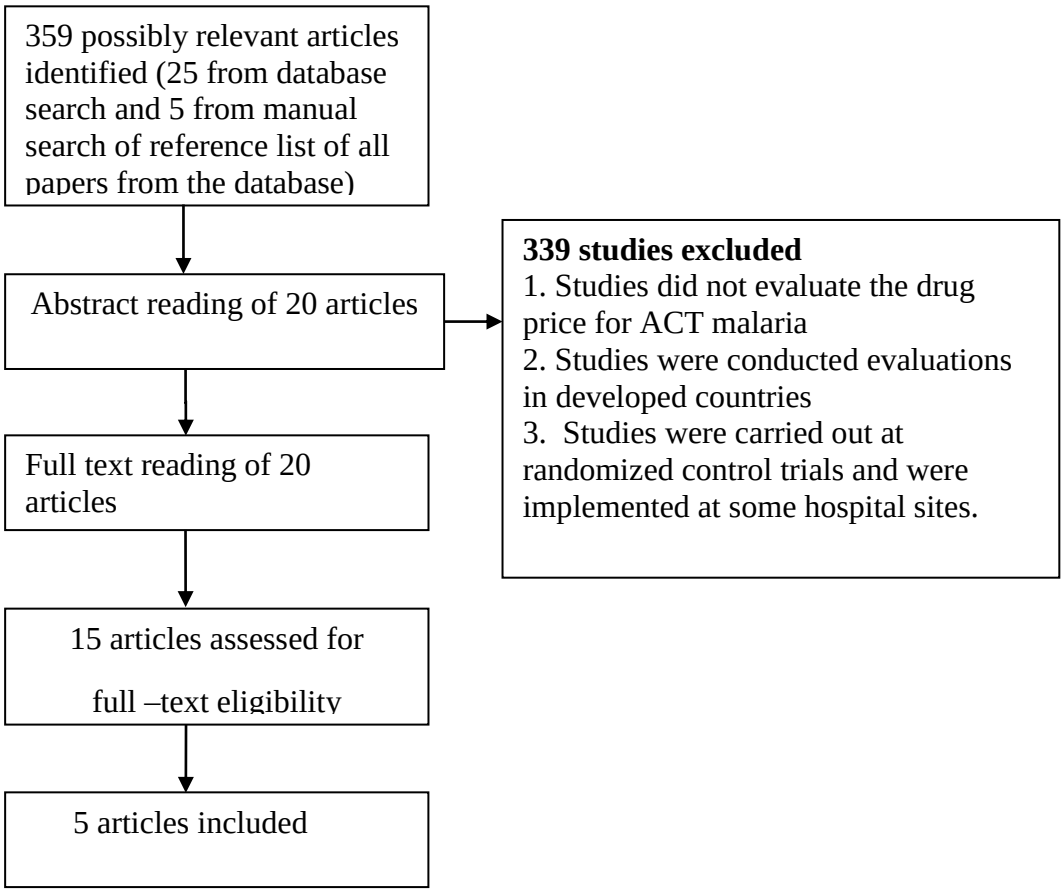
Differences in survival times (days) for immediate ART strategy versus deferred ART strategy



Appendix 12: **Key search term for program costs for malaria project**

Database	Keywords	Results
PUBMED	#1 (cost OR costs) AND (revis(ed) OR revising OR introducing OR introduction OR introduce OR switch OR switching OR changing OR change OR implementing OR implementation OR replacing OR replacement) AND (first-line drug) AND malaria #2 (malaria [title] OR first-line drug [title] OR drug policy [title]) AND (revise OR revising OR introducing OR introduction OR introduce OR switch OR switching OR changing OR change OR implementing OR implementation OR replacing OR replacement) AND (cost OR costs[title/abstract] OR cost-effective* OR cost-utility* OR cost-benefit*) AND (analysis OR "economic evaluation*") #3 (Cost-effectiveness analysisORcost-benefit analysisOR cost- utility analysis OR economic evaluation) AND (malaria) AND (revise OR revising OR introducing OR introduction OR introduce OR switch OR switching OR changing OR change OR implementing OR implementation OR replacing OR replacement) AND (first-line drug OR drug policy)	565 hits 49 hits 160 hits 27 hits
SOLO	#1 (Cost OR costs) AND (revise OR revising OR introducing OR introduction OR introduce OR switch OR switching OR changing OR change OR implementing OR implementation OR replacement OR replacing) AND (first-line drug OR drug policy) #2 (malaria) AND (first-line drugs OR drug policy) AND (revise OR revising OR introducing OR introduction OR introduce OR switch OR switching OR changing OR change OR implementing OR implementation OR replacing OR replacement) AND (cost or costs or cost-effective* or cost-utility* or cost-benefit*) AND (analysis or "economic evaluation*") #3 (Cost-effectiveness analysis or cost-benefit analysis or cost-utility analysis or economic evaluation) AND(malaria) AND (first-line drugs OR drug policy) AND (revise OR revising OR introducing OR introduction OR introduce OR switch OR switching OR changing OR change OR implementing OR implementation OR replacing OR replacement)	181 hits
NHS-ED	"costs" AND " introducing" OR "changing" OR" switching " OR "implementing" AND "first-line drug(s)" OR "drug policy" (any field)	2
	"cost" AND "drug policy"	10
	"cost" AND "first-line drugs"	4
	"costs" AND "combination therapies"	50

Appendix 13**: Flow chart of search strategy for the ACT drug costs**



Appendix 14: **The assumption of unit costs for different strategies**

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	**MFT strategy**		**Distribution**	
		Unit cost (range)	Percent increase over single first-line drugs		
Set-up costs (non-recurrent costs)					
Activity 1: Policy formulation: This includes activities such as planning, policy related consultations and advisory meetings, consensus building	63,152 (+ - 20%)	289,163 (+/- 20%)	358%	Triangle	For the cycling/sequential strategy, the costs of activity 1 were substituted by the costs of the project team recruitment, consultation and planning, plus the office equipment $63,152 (2013 USD) per year [198]This value was derived from the costs of the switch from CQ to SP in Tanzania [198] For MFT strategy, the costs of the project team recruitment, consultation and planning were increased to $289.163 (2013 USD). This value was obtained from scenario of strengthening the implementation team for the national drug policy change [197]
Activity2: Revision & production &printing & distribution of IEC, drug packages and health materials .	0.0017 (min= 0.0015 max = 0.004)	0.002 (+/- 20%)	10%	Triangle	For cycling and sequential strategy, the costs of activity 2 were equal to $0.0017 (0.0015 to 0.004) per person per year. The average costs of the revision and printing from 3 studies that evaluated the switch from CQ to SP [181,198,205] For the MFT strategy, the cost of printing and revision associated with the cycling and sequential strategy was assumed to increase by 10% to reflect the scenario where more guidelines were distributed at districts [198]

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	MFT strategy		Distribution	
		Unit cost (range)	Percent increase over single first-line drugs		
Activity 3: Training of health personnel -Training health personnel in formal health facilities -Setting up and training community health workers	0.01 (min = 0.005 max = 0.02) 0.81 (+/-20%)	0.03 (min= 0.002 max=0.07) 1.27 (+/20%)	160% 59%	Triangle	For cycling and sequential strategy, the training cost per person (including training of health personnels, trainers and supervisors) was equal to \$0.01 (\$0.005 to \$0.02) . This value was derived from the average costs, min and max costs of the switch from CQ to SP of 3 studies [181,198,205] For cycling and sequential strategy, the basic annual fixed costs of setting-up and training the outreach team was assumed to be \$0.81 per person (2013 USD) [206] For MFT strategy, the cost of training health personnels per person was equal to \$0.03 (\$0.002 to \$0.07) which was obtained from the average costs of the switch from SP to ACT in 7 scenarios in Tanzania [197] For perfect MFT strategy, the cost of training health village workers per person was equal to \$1.27 (2013 USD) [206]
Activity 4: Information, education, and communication (IEC).	0.007 (min=0.001 max= 0.02)	0.11 (min= 0.008 max= 0.05)	1456%	Triangle	For cycling and sequential strategy, the cost of IEC were equal to 0.007 (0.001 to 0.02) per person per year. This value was derived from the average costs, min and max costs of the switch from CQ to SP of 3 studies ([181,198,205] For MFT strategy, the cost per person was \$0.07 (0.002 to 0.05) which was

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	MFT strategy		Distribution	
		Unit cost (range)	Percent increase over single first-line drugs		
					obtained from the average, min and max costs of the switch from SP to ACT n 7 scenarios in Tanzania [197]
Activity 5:Program management and monitoring and evaluation (M/M&E)	0.003 (min= 0.001 max= 0.007)	0.02 (min=0.001 max =0.05)	628%	Triangle	For cycling and sequential strategy, the cost of revision and printing were equal to $0.003 (0.001 to 0.007) per person per year. This value was derived from the average costs, min and max costs of the switch from CQ to SP of 3 studies [181,198,205] For MFT strategy, the cost per person $0.02 (0.001 to 0.05) which was obtained from the average costs of the switch from SP to ACT n 7 scenarios in Tanzania [197]
Recurrent costs					
Activity 6: **Drug purchase**	1% volume discount	0.3% volume discount		Triangle	A volume discount is reduced to a third if the drug assortment for a treatment is increased to 3 drugs. [179]
Unit drug price per full treatment course for uncomplicated malaria (3 days) DHAPPQ(40+320mg tab-cap) Group1 (2 tablets) Group 2 (4 tablets) Group 3 (6 tablets) Group 4 (8 tablets)	 0.436 0.871 1.307 1.742	 0.439 0.877 1.316 1.754		Triangle	Unit drug prices per DHA-PPQ, ASAQ, & AL tablet were obtained from (Global fund 2013). Dosage treatment are extracted from Vietnamese national treatment guidelines 2013) & Tanzania treatment guidelines 2013) and WHO guidelines 2010). A volume discount of 1% per treatment course was assumed for cycling/sequential strategy and 0.3% for the MFT strategy [179] .
AL (20mg + 120mg tab-cap) Group1 (6 tablets) Group 2 (12 tablets) Group 3 (18 tablets) Group 4 (24 tablets)	 0.285 0.570 0.855 1.14	 0.287 0.574 0.86 1.148			
AS-AQ (50mg+153mg tab-cap) Group 1 (1.5 tablets) Group 2 (3 tablets)	0.0861 0.172 0.345 0.689	0.0867 0.173 0.347 0.694			

Activities	Unit cost for strategies				References for unit costs
	Cycling/ Sequential strategy	MFT strategy		Distribution	
		Unit cost (range)	Percent increase over single first-line drugs		
Group 3 (6 tablets) Group 4 (12 tablets)					
Drug delivery costs per uncomplicated case (including storage, distribution, training, and management) from the central-level to health facilities-level	20% of the drug price	40% of the drug price	100%	Triangle	For cycling/sequential strategy, the cost of delivering the drugs was assumed to be 20% of the drug price. This is the average cost of delivering ACT from the central-level to health facilities level in Benin and Kenya[218] For MFT strategy, the cost of delivering drugs was assumed to double the cost of delivering drugs in the cycling/sequential strategy
Activity 7: **Case-management** Direct costs of an uncomplicated malaria case at formal-sector facilities The cost of second line treatment The average costs of treating adult severe case (>5 years old) and children severe case (≤ 5 years old)	5.84 (range 2.36-23.65) 21 64.50 (26.99 to 288.79)			Triangle Fixed value Triangle	These costs of outpatient visit included an outpatient consultant, and the patient cost such as travel costs, medical supplies, non-medical supplies (excluding fixed costs and drug costs) 5.84 (range 2.36-23.65) (2009 USD) [255] The cost of second-line quinine is 16.32 (2009 USD) or 21 (2013 USD) [174] 64.50 (26.99 to 288.79) (2009 USD) is the median economic cost of treating severe cases in White (2009) [255]

Appendix 15:**Assumptions of drug price of ACT**

Artemether-lumefantrine (AL), artesunate-amodiaquine (ASAQ), and dihydroartemisinin-piperaquine (DHA-PPQ) by tablets and costs (2013 US values)

Drug	Unit price	Reference
Artemether-lumefantrine (AL) AL 20mg + 120mg tab-cap	0.048/tab-cap (18 tab- FDC)	The Global Fund price and quality report [256]
Artesunate-amodiaquine (ASAQ) AS-AQ 50mg+153mg tab-cap	0.058/tab-cap (6+6 tab co-blister)	
Dihydroartemisinin-piperaquine (DHA-PPQ) DHA-PPQ 40mg+320mg tab-cap	0.220 tab-cap (9 tab–FDC)	

Dosage regimen to treat uncomplicated malaria for AL, DHA-PPQ, and AS-AQ

DHA-PPQ (Arterakine, CV Artecan) 40mg x 320mg Vietnamese national treatment guidelines 2009[257]			
Age-groups	**Day 1**	**Day 2**	**Day 3**
< 3 years	1 tablet (1 /2 tablet separated by 8 hours)	½ tablet	½ tablet
3 – 8 years	2 tablets (a tablet separated by 8 hours)	1	1
8 – 15 years	3 tablets (1 ½ tablet separated by 8 hours)	1 ½	1 ½

Dosage regimen to treat uncomplicated malaria for AL, DHA-PPQ, and AS-AQ

DHA-PPQ (Arterakine, CV Artecan)40mg x 320mg (Tanzania treatment guidelines 2005) [257]			
Age-groups	**Day 1**	**Day 2**	**Day 3**
< 3 years	1 tablet (1 /2 tablet separated by 8 hours)	½ tablet	½ tablet
3 – 8 years	2 tablets (a tablet separated by 8 hours)	1	1
8 – 15 years	3 tablets (1 ½ tablet separated by 8 hours)	1 ½	1 ½
Over 15 years	4 tablets (2 tablets separated by 8 hours)	2 tablets	2 tablets
AL (Coartem®, Novartis Pharma AG, Basel, Switzerland) 20mg + 120mg tab-cap [258]			
Age-groups	**Day 1**	**Day 2**	**Day 3**
3 months – 3 years	2tablets(1 tablet separated by 8 hours)	2 tablets (1 tablet separated by 12	2 tablets (1 tablet separated by 12

		hours)	hours)
3 -8 years	4 tablets (2 tablet separated by 8 hours)	4 tablets (2 tablets separated by 12 hours)	4 tablets (2 tablets separated by 12 hours)
8-12 years	6 tablets (3 tablets separated by 8 hours)	6 tablets (3 tablets separated by 12 hours)	6 tablets (3 tablets separated by 12 hours)
Over 12 years	8 tablets (4 tablets separated by 8 hours)	8 tablets (4 tablets separated by 12 hours)	8 tablets (4 tablets separated by 12 hours)
AS-AQ (Coarsucam) 50mg+153mg tab-cap [259]			
Age-groups	**Day 1**	**Day 2**	**Day 3**
2 -11 months	½ tablet	½ tablet	½ tablet
1-5 years	1 tablet	1 tablet	1 tablet
6-13 years	2 tablets	2tablets	2 tablets
Over 14 years	4 tablets	4 tablets	4 tablets

Appendix 16: **The average total costs for different treatment strategies of malaria**

The predicted total costs for a population of 1 million people during 20 years period for different treatment strategies and the median differences in total costs with 95% confidence intervals across treatment coverage (50%, 60%, 70%, 80%, 90%) and fitness cost of resistance (0.001, 0.005, 0.01). The pairs of strategies that are being compared MftCy (the MFT strategy versus the 5 year-cycling strategy), MftSeq (the MFT strategy versus the sequential strategy). The total costs cover the set-up costs, the drug costs, and the case management costs. These costs present in low transmission settings (1.3 infectious bites per person per year) and high transmission settings (20.3 infectious bites per person per year). The costs are in million US dollars in year 2013.

Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean)	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)	Number of policy changes in sequential strategy (median)
0.5	0.001	2,725,144	2,872,913	3,114,909	-396,278 (-420,763 -376,693)	-145,120 (-170,338 -118,415)	5
0.5	0.005	2,635,061	2,777,119	2,899,099	-237,630 (-280,705 -208,920)	-140,729 (-154,536 -122,502)	2
0.5	0.01	2,594,004	2,720,584	2,758,838	-159,618 (-179,054 -141,366)	-126,439 (-146,202 -106,631)	1
0.6	0.001	2,311,442	2,493,479	2,709,850	-373,516 (-414,150 -320,829)	-169,329 (-221,156 -119,736)	6
0.6	0.005	2,148,068	2,303,534	2,545,812	-362,703 (-392,848 -336,367)	-154,219 (-179,481 -129,200)	5
0.6	0.01	1,988,028	2,122,416	2,328,513	-372,688 (-395,551 -344,569)	-141,705 (-156,944 -124,294)	2
0.7	0.001	1,937,969	2,119,396	2,402,002	-486,935 (-539,278 -414,542)	-156,184 (-193,974 -120,390)	7
0.7	0.005	1,750,583	1,923,796	2,174,431	-438,446 (-484,976 -379,816)	-133,841 (-180,384 -96,764)	7
0.7	0.01	1,537,031	1,723,651	1,972,138	-398,465 (-452,782 -350,315)	-158,414 (-187,938 -134,862)	5

Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean)	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)	Number of policy changes in sequential strategy (median)
0.8	0.001	1,593,552	1,749,554	2,039,337	-455,175 (-504,895 -411,527)	-143,809 (-220,978 -84,510)	8
0.8	0.005	1,337,667	1,565,410	1,783,647	-449,619 (-504,644 -384,363)	-188,264 (-247,676 -142,984)	7
0.8	0.01	1,115,973	1,272,140	1,535,515	-394,771 (-477,402 -329,972)	-115,803 (-174,109 -66,506)	7
0.9	0.001	771,602	1,000,771	1,245,226	-492,626 (-823,698 -311,112)	-234,603 (-575,037 -51,817)	8
0.9	0.005	532,438	892,868	1,109,897	-848,742 (-1,189,258 -517,731)	-591,593 (-907,771 -299,142)	8
0.9	0.01	399,105	647,182	652,891	-403,946 (-661,682 -55,743)	-413,862 (-660,806 -151,720)	8

Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean))	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)	Number of policy changes in sequential strategy (median)
0.5	0.001	4,987,211	5,143,272	5,394,919	-413,163 (-447,385 -383,832)	-155,754 (-190,485 -125,935)	5
0.5	0.005	4,907,214	5,024,237	5,183,327	-271,796 (-297,165 -250,173)	-115,898 (-145,150 -91,959)	2
0.5	0.01	4,880,678	5,020,172	5,092,369	-216,254 (-246,565 -190,674)	-144,497 (-179,107 -112,620)	1
0.6	0.001	4,774,195	4,974,729	5,270,687	-471,072 (-498,854 -443,090)	-186,204 (-215,913 -154,381)	6
0.6	0.005	4,526,706	4,684,569	5,031,789	-513,558 (-540,771 -485,945)	-152,830 (-174,345 -128,044)	5

Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean))	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)	Number of policy changes in sequential strategy (median)
0.6	0.01	4,445,388	4,577,408	4,765,383	-311,538 (-334,811 -290,647)	-118,351 (-140,037 -99,050)	2
0.7	0.001	4,740,450	4,973,956	5,291,028	-532,601 (-587,784 -482,342)	-220,949 (-259,228 -185,114)	7
0.7	0.005	4,323,882	4,560,861	4,938,422	-575,599 (-607,491 -539,994)	-229,628 (-254,001 -203,143)	7
0.7	0.01	4,063,222	4,226,171	4,625,603	-569,935 (-588,103 -552,052)	-162,271 (-180,855 -139,658)	5
0.8	0.001	4,762,253	5,057,576	5,376,243	-623,579 (-643,724 -604,441)	-303,064 (-325,399 -280,958)	8
0.8	0.005	4,277,805	4,609,943	5,041,564	-776,293 (-812,435 -749,153)	-325,152 (-360,896 -295,605)	7
0.8	0.01	3,823,036	4,133,228	4,581,667	-740,484 (-781,755 -693,573)	-307,472 (-326,641 -286,232)	7
0.9	0.001	4,852,462	5,161,450	5,400,508	-537,866 (-575,169 -502,532)	-301,843 (-346,693 -249,716)	8
0.9	0.005	4,346,769	4,752,079	5,060,257	-712,040 (-737,512 -688,477)	-420,139 (-459,615 -38,1851)	8
0.9	0.01	3,802,400	4,270,261	4,724,986	-949,581 (-966,125 -933,671)	-437,373 (-463,765 -404,273)	8

Appendix 17: **The average disability adjusted life years (DALYs) for different treatment strategies of malaria**

The predicted years lived with disability (DALYs) for a population of 1 million people during 20 years period for different treatment strategies and the median differences in DALYs with 95% confidence intervals across treatment coverage (50%, 60%, 70%, 80%, 90%) and fitness cost of resistance (0.001, 0.005, 0.01). The pairs of strategies that are being compared are CySeq (the 5 year-cycling strategy versus the sequential strategy), MftCy (the MFT strategy versus the 5 year-cycling strategy), MftSeq (the MFT strategy versus the sequential strategy). The DALYs comprise the years life lost (YLLs) and the years lived with disability (YLDs). These DALYs present in low and high transmission setting (1.3 and 20.3 infectious bites per person per year). The DALYs are in 100,000 units.

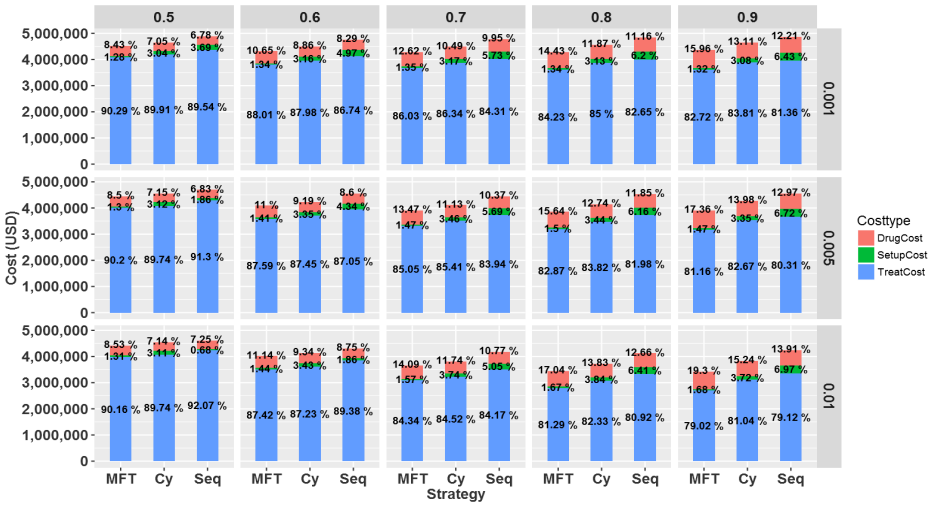
Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean))	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)
0.5	0.001	48,180.2	49,463.7	51,395.0	-3,206.4 (-3,452.9 -2,910.1)	-1,287.5 (-1,560.2 -992.7)
0.5	0.005	47,118.2	48,165.1	49,985.5	-2,837.1 (-3,070.7 -2,548.5)	-1,048 (-1,213.1 -855.5)
0.5	0.01	46,742.0	47,749.3	50,140.9	-3,385.4 (-3,469.4 -3,277.5)	-1,001.5 (-1,125.9 -860.2)
0.6	0.001	36,193.5	37,422.2	37,932.3	-1,703.7 (-1,998.2 -1,389.9)	-1,200.7 (-1,744.4 -816.1)
0.6	0.005	34,230.8	35,431.0	36,472.9	-2,250 (-2,519.5 -1,939.5)	-1,184.9 (-1,489.3 -850)
0.6	0.01	32,496.1	33,506.5	35,420.9	-2,925.7 (-3,114.5 -2,729.4)	-1,011.8 (-1,153.9 -868)
0.7	0.001	25,459.6	26,231.4	27,874.6	-2,410.7 (-2,669 -2,020.9)	-794.7 (-1,146.7 -443.2)
0.7	0.005	23,357.5	24,253.7	25,615.9	-2,262 (-2,707 -1,438.4)	-896.2 (-1,191.7 -531.2)
0.7	0.01	21,243.3	22,209.6	22,923.7	-1,678.2 (-2,131.8 -1,462.6)	-982.1 (-1,226 -767.7)

Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean))	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)
0.8	0.001	16,319.9	16,597.5	17,802.3	-1,514.9 (-1977.2 -1,022.1)	-294.8 (-938 - 152.4)
0.8	0.005	14,170.7	14,762.7	15,568.4	-1,439.6 (-1,973.2 -996.4)	-627.1 (-1,123.6 -203.9)
0.8	0.01	12,088.1	12,134.4	13,264.6	-1,204.3 (-1,831.5 -608.9)	-58.1 (-574.4 -266.7)
0.9	0.001	7,428.9	8,167.0	8,417.6	-1,034.6 (-3,480.1 -15.7)	-760.3 (-3,296.1 -496.2)
0.9	0.005	3,219.1	6,850.7	7,218.8	-3,818.1 (-6,589.8 -1,516.2)	-3,433 (-6,049.4 -1,397.3)
0.9	0.01	2,326.2	4,627.0	3,552.0	-1,054.5 (-3,291.9 1,454.9)	-2,122.1 (-4,251.6 -221.4)

Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean)	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)
0.5	0.001	199,230.0	205,818.3	212,953.0	-13,747.1 (-14,099.7 -13,464.9)	-6,610 (-6,909 -6,380.1)
0.5	0.005	198,646.2	205,248.1	217,096.9	-18,445.9 (-18,867.5 -17,990.4)	-6,598.1 (-6,823.4 -6,331.1)
0.5	0.01	198,595.4	205,200.2	218,760.3	-20,155.8 (-20,434.7 -19,888)	-6,571 (-6,866.8 -6,236.4)
0.6	0.001	161,916.2	168,271.3	171,491.1	-9,571.2 (-10,142.4 -9,236)	-6,393.7 (-6,663.9 -6,165.1)
0.6	0.005	160,354.3	166,781.7	172,918.8	-12,578.5 (-13,176 -12,276.7)	-6,402.9 (-6,629.5 -6,159.7)
0.6	0.01	160,091.3	166,374.6	177,337.9	-17,245.1 (-17,631.8 -16,833.2)	-6,254.4 (-6,500.6 -5,950)
0.7	0.001	126,667.5	132,655.6	134,441.3	-7,757 (-8,119.8 -7,312.2)	-5,993 (-6,256.3 -5,804.7)
0.7	0.005	124,649.7	130,640.9	132,429.1	-7,782.8 (-8,151.8 -7,444.7)	-6,018.6 (-6,316.9 -5,750.7)

Treatment coverage	Fitness Cost of resistance	MFT strategy (mean)	Cycling strategy (mean)	Sequential strategy (mean)	MFT-SEQ (mean) (95% CIs)	MFT-CY (mean) (95% CIs)
0.7	0.01	123,744.5	129,490.1	134,851.6	-11,137.6 (-11,542.3 -10,901.3)	-5,735.7 (-5,911.2 -5,578.4)
0.8	0.001	933,82.9	98,605.0	100,481.5	-7,089 (-7,254.2 -6,900.6)	-5,224.3 (-5,434.5 -5,051.8)
0.8	0.005	91,411.1	96,552.7	98,651.1	-7,240.1 (-7,481 -70,12.5)	-5,134.7 (-5,298 -4,970.9)
0.8	0.01	90,234.4	95,153.9	96,467.8	-6,267 (-6,515.2 -6,058.1)	-4,958.8 (-5,164.8 -4,821.2)
0.9	0.001	61,949.5	65,908.2	66,754.1	-4,818.7 (-5,012.2 -4,665)	-3,966.4 (-4,175.5 -3,760)
0.9	0.005	60,298.6	64,388.0	65,345.5	-5,054.7 (-5,191.8 -4,922.6)	-4,090.1 (-4,212.5 -3,941.3)
0.9	0.01	59,215.2	63,101.2	64,593.1	-5,391.5 (-5,588.1 -5,105.9)	-3,886 (-4,072.9 -3,681.2)

Appendix 18**: The structure of total costs for different strategies**



The structure of the discounted total cost for different strategies, different costs of resistance (CR), and different treatment coverages (f) in a low transmission settings with an entomological inoculation rate of 1·3 (first graph) and high transmission settingwith an entomological inoculation rate of 20·3 (second graph). The costs are in 2013 US dollars. The figure contains 15 scenarios corresponding to different treatment coverage levels (50% to 60% to 70% to 80% to 90%), and different biological fitness costs for drug-resistant genotypes (50% to 60% to 70% to 80% to 90%) from left to right in the panels. The *y*-axis shows the median total costs per one million population during the 20-year simulation, discounted at 3%. The x-axis presents the 3 strategies that are being compared: the MFT strategy, 5 year-cycling strategy, sequential strategy. The colours refer to the cost types which are the drug costs (red), set-up costs (green), the case-management costs (blue). The case management costs were the main component across all the scenarios.

Appendix 19: **Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis**

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Timing of Initiation of Antiretroviral Therapy in Human Immunodeficiency Virus (HIV)–Associated Tuberculous Meningitis

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Abstract

Background—The optimal time to initiate antiretroviral therapy (ART) in human immunodeficiency virus (HIV)–associated tuberculous meningitis is unknown.

Methods—We conducted a randomized, double-blind, placebo-controlled trial of immediate versus deferred ART in patients with HIV-associated tuberculous meningitis to determine whether immediate ART reduced the risk of death. Antiretroviral drugs (zidovudine, lamivudine, and efavirenz) were started either at study entry or 2 months after randomization. All patients were treated with standard antituberculosis treatment, adjunctive dexamethasone, and prophylactic co-trimoxazole and were followed up for 12 months. We conducted intention-to-treat, per-protocol, and prespecified subgroup analyses.

Results—A total of 253 patients were randomized, 127 in the immediate ART group and 126 in the deferred ART group; 76 and 70 patients died within 9 months in the immediate and deferred ART groups, respectively. Immediate ART was not significantly associated with 9-month mortality (hazard ratio [HR], 1.12; 95% confidence interval [CI], .81–1.55; $P = .50$) or the time to new AIDS events or death (HR, 1.16; 95% CI, .87–1.55; $P = .31$). The percentage of patients with severe (grade 3 or 4) adverse events was high in both arms (90% in the immediate ART group and

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89% in the deferred ART group; $P = .84$), but there were significantly more grade 4 adverse events in the immediate ART arm (102 in the immediate ART group vs 87 in the deferred ART group; $P = .04$).

Conclusions—Immediate ART initiation does not improve outcome in patients presenting with HIV-associated tuberculous meningitis. There were significantly more grade 4 adverse events in the immediate ART arm, supporting delayed initiation of ART in HIV-associated tuberculous meningitis.

Clinical Trials Registration—ISRCTN63659091.

Tuberculosis is the most common coinfection in individuals infected with human immunodeficiency virus (HIV) and a major cause of morbidity and mortality. The optimal time to initiate antiretroviral therapy (ART) in patients presenting with HIV infection and tuberculosis remains controversial. Early initiation of ART, with antituberculosis therapy, may be associated with overlapping drug toxicities, drug–drug interactions, and immune reconstitution inflammatory syndrome (IRIS), which are all potentially detrimental. Conversely, delayed initiation may result in HIV disease progression and death. Current guidelines [1-3] recommend initiation of ART between 2 and 8 weeks in patients presenting with HIV infection and tuberculosis.

Tuberculous meningitis (TBM) is the most severe form of tuberculosis, killing or disabling more than half of those affected [4]. HIV-associated TBM has a similar clinical presentation [5-7] but higher mortality [8, 9]. The management of TBM is problematic because early initiation of ART may be complicated by a central nervous system (CNS) IRIS, leading to neurological deterioration or death. Thus, the optimal time to initiate ART may differ for TBM compared with that for extracranial tuberculosis. We conducted a randomized, controlled trial of immediate versus deferred initiation of ART in patients with HIV infection and TBM, to determine whether immediate ART reduced the risk of death.

METHODS

Study Design

The study was a randomized, double-blind, placebo-controlled trial with 2 parallel arms: immediate ART (initiated within 7 d of commencing tuberculosis treatment) and deferred ART (initiated after 2 months of tuberculosis treatment).

Sample Size Calculation

The case-fatality rate for patients with HIV-associated TBM in 2 previous studies was 65% [8, 9]. We calculated that 222 patients would be required to provide at least 80% power to detect a 30% reduction in mortality at 9 months from 65% to 45.5%, with a 2-sided significance level of 5%. In order to allow for a 10% loss to follow-up we aimed to recruit 247 patients.

Study Participants and Laboratory Investigations

Study participants were recruited at Pham Ngoc Thach Hospital and the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. Cerebrospinal fluid (CSF) specimens were

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stained and cultured by standard methods for pyogenic bacteria, fungi, and mycobacteria. Isolates of *Mycobacterium tuberculosis* were tested for susceptibility to first-line agents. All patients were tested for antibodies to HIV and hepatitis C virus (HCV) and for hepatitis B virus (HBV) surface antigen. CD4 cell counts were performed by flow cytometry (FACSCalibur; Becton Dickinson). Plasma HIV RNA loads were determined using the Abbott RealTime HIV-1 assay (Abbott Laboratories).

Inclusion and Exclusion Criteria

Patients were eligible for the trial if they were aged 15 years and HIV infected and fulfilled diagnostic criteria for TBM, as described elsewhere [9]. Patients were categorized as having definite, probable, or possible TBM. Patients were classified as having definite TBM if the CSF specimen was smear positive for acid-fast bacilli and/or culture positive for *M. tuberculosis*. Patients were classified as having probable TBM if they fulfilled 1 of 4 criteria: chest radiograph consistent with pulmonary tuberculosis, other specimens (eg, sputum, lymph node, or gastric washings) that were positive for acid-fast bacilli, evidence of extrapulmonary tuberculosis, or radiological features of TBM on computed tomographic or magnetic resonance imaging scan. Patients were classified as having possible TBM if they fulfilled 2 of 4 criteria (past history of tuberculosis, illness duration of >5 days, Glasgow coma score (GCS) of <15, or focal neurological signs) and 2 of 3 further criteria (yellow CSF, >50% of lymphocytes in the CSF, or CSF glucose level <50% of the blood glucose level).

TBM disease severity was assessed using the modified Medical Research Council (MRC) TBM grade, as described elsewhere [4]. Grade I TBM was defined as a GCS of 15 with no focal neurology, grade II TBM as a GCS of 15 with a focal neurological deficit or a GCS of 11–14, and grade III TBM as a GCS of 10.

Patients were ineligible for the trial if they had 1 or more of the following exclusion criteria: positive CSF Gram or India ink stain; known or suspected pregnancy; antituberculosis treatment 8–30 d immediately prior to recruitment; previous ART; laboratory contraindications to ART or antituberculosis therapy (hemoglobin level of <7.0 g/dL, blood neutrophil count of $<.5 \times 10^9$ cells/L, serum creatinine level >3 times the upper limit of normal [ULN], serum bilirubin level >2.5 times the ULN, or serum transaminase level >5 times the ULN); or lack of consent.

Consent Procedures

Written informed consent was obtained from the patient or a relative if the patient could not provide consent. For unconscious patients with no available relatives, the consent of 2 independent physicians was considered acceptable. Patients who recovered consciousness reconsented to the study.

Randomization Procedures

Stratified variable block randomization according to modified MRC TBM grade at presentation was used to assign participants to the 2 treatment groups. Antiretroviral or

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placebo tablets were placed in coded, sealed boxes; drug appearance and administration schedules were identical to maintain blinding among attending physicians and nurses.

Treatments

In adults previously untreated for tuberculosis, initial therapy was with oral isoniazid at a dose of 5 mg/kg (maximum dose, 300 mg/d), rifampicin at a dose of 10 mg/kg (maximum dose, 600 mg/d), pyrazinamide at a dose of 25 mg/kg (maximum dose, 2 g/d), and ethambutol at a dose of 20 mg/kg (maximum dose, 1.2 g/d), once daily for 3 months. After 3 months, pyrazinamide and ethambutol were stopped and the patient continued treatment with rifampicin and isoniazid at the same doses for another 6 months. Intramuscular streptomycin (dose, 20 mg/kg; maximum dose, 1g/d) was added to the initial treatment regimen of patients previously treated for tuberculosis. Second-line antituberculosis therapy was un-available during the study.

Unless it was contraindicated, all patients received dexamethasone at an initial dose of .3–.4 mg/kg/d, according to modified MRC TBM grade at presentation, and tapered over 6–8 weeks, as described elsewhere [4].

Antiretroviral or placebo tablets were commenced as soon as possible after randomization. The antiretroviral regimen was oral zidovudine (GlaxoSmithKline) at a dose of 300 mg twice daily, lamivudine (GlaxoSmithKline) at a dose of 150 mg twice daily (as a fixed-dose combination tablet), and efavirenz (Merck) at a dose of 800 mg once daily (if taken with rifampicin) or efavirenz at a dose of 600 mg once daily (if taken without rifampicin). Placebos were manufactured by GlaxoSmithKline (zidovudine and lamivudine placebo) and Brecon Pharmaceuticals (efavirenz placebo). After 2 months, all patients received antiretroviral drugs until the end of the study period (12 months).

All patients with a baseline CD4 cell count of <200 cells/μL received oral co-trimoxazole at a dose of 960 mg daily after 4 weeks [10].

Medications were administered orally or via nasogastric tube. Patients received directly observed therapy during their inpatient stay (up to 3 months); administration was supervised by family members after hospital discharge.

Patient Monitoring

The study physicians reviewed inpatients daily and completed a weekly standard assessment. As outpatients, participants were assessed monthly until 9 months and at 12 months after randomization.

Routine laboratory tests were monitored weekly for inpatients and monthly for outpatients. CD4 cell counts and plasma HIV-1 RNA levels were measured 3 times each month. CSF samples were taken at baseline and at 1, 2, 3, 6, 9, and 12 months.

Outcome Assessment

The primary outcome was the time from randomization to death in the first 9 months of follow-up. Patients who did not die were censored at the time they were last known to be alive or at 9 months, whichever was earlier.

Secondary outcome measures were time to death during the 12-month follow-up period, HIV-related outcomes (CD4 cell count response, HIV-1 RNA load response, and time to new or recurrent AIDS-defining illness or death), and other secondary outcomes, including time to fever clearance (defined as a maximum daily temperature of <37.5°C for at least 6 consecutive days), time to coma clearance (GCS of 15 for at least 3 consecutive days), time to first neurological event (defined as any neurological deterioration, coma, seizures, cranial nerve palsy, hemiplegia, paraplegia, cerebellar symptoms or cerebral herniation, or decrease in GCS of 2 points from the highest previously recorded score for at least 2 d or for 1 d plus subsequent death) or death, any grade 3 or 4 adverse event, and neurological disability. Adverse events were graded using the Division of AIDS Table for Grading of Severity of Adult and Paediatric Adverse events. Neurological disability was assessed using the 2 simple questions and modified Rankin scale and classified as good, intermediate, severe disability, or death, as described elsewhere [4].

Study Oversight

The trial was approved by the hospitals' institutional review boards and the Oxford Tropical Research Ethics Committee. A Data and Safety Monitoring Committee oversaw conduct of the trial and reviewed adverse event and mortality data after 20 deaths, then after 6, 12, and 18 months of recruitment, and at the end of recruitment. The trial was not stopped early.

Statistical Analysis

The primary endpoint was compared between the groups by means of the log-rank test and visualized with Kaplan-Meier curves. The analysis was repeated in prespecified subgroups (TBM disease grade, TBM diagnostic category, CD4 cell count at baseline, and HIV-1 RNA load at baseline) and in the per-protocol population. The per-protocol population excluded major protocol violators and patients who withdrew consent or were lost to follow-up. The primary endpoint was also analyzed with a Cox regression analysis adjusted for the following baseline variables: TBM disease grade, CD4 cell count, HIV-1 RNA load, hemoglobin level, and serum sodium level.

Analyses of time to new or recurrent AIDS event or death, and time to first neurological event or death, were perfomed as for the primary endpoint. The cumulative incidence functions of patients achieving HIV-1 RNA suppression, fever clearance, or coma clearance were compared between the 2 arms using the Fine and Gray regression model [11], taking into account the competing risk of prior death. We compared CD4 cell count change from baseline at months 2 and 12 in survivors by use of the Mann-Whitney *U* test. The number of patients with adverse events in each arm was compared using the Fisher exact test. Disability scores at month 12 were compared using a linear trend test.

Multiple imputation was used to account for missing baseline variables and missing follow-up HIV RNA load, CD4 cell count, and disability status measurements. All adjusted regression analyses were based on imputed data.

All analyses were performed with the statistical software R (version 2.8.1; R Foundation for Statistical Computing) [13] and the contributed R packages MICE (for multiple imputation) and cmprsk (for competing risk analyses).

RESULTS

There were 703 patients screened between 20 September 2005 and 28 December 2007 (Figure 1); 253 participants were randomly assigned to immediate ART (127 patients) or deferred ART (126 patients), and 38 patients (19 in each group) were excluded after randomization from the per-protocol analysis (Figure 1).

Twenty-eight patients withdrew or were lost to follow-up after a median of 82 days (interquartile range, 24–158 days). The distribution of age, sex, disability status, GCS, TBM grade, CD4 cell count, and HIV-1 RNA load at baseline was similar to that in patients who remained in the study.

Baseline Characteristics

Patient characteristics at randomization were similar in the 2 treatment arms (Table 1). Study participants were predominantly young, male, and intravenous drug users. The median baseline CD4 cell count was 41 cells/μL, and the median baseline plasma HIV-1 RNA level was 5.4 $\log_{10}$ copies/mL.

Primary Endpoint

In the first 9 months after randomization, 76 patients in the immediate ART group and 70 in the deferred ART group died (hazard ratio [HR] of immediate versus deferred ART, 1.12; 95% confidence interval [CI], .81–1.55; $P = .50$). The majority of deaths (45 in the immediate ART group and 40 in the deferred ART group) occurred within the first month. The results of the per-protocol analysis were similar to those of the intention-to-treat analysis. There was no evidence for heterogeneity of the treatment effect in any of the prespecified subgroups (Table 2 and Figure 2).

Immediate ART was not associated with improved 9-month survival (HR, 1.17; 95% CI, .85–1.63; $P = .34$) in the multiple Cox regression analysis. Baseline TBM disease grade was a strong independent predictor for death (HR for TBM grade II, 1.66; 95% CI, 1.07–2.57; $P = .02$ compared with TBM grade I; HR for TBM grade III, 3.42; 95% CI, 2.29–5.33; $P < .001$ compared with TBM grade I). Other baseline variables such as CD4 cell count per 100 cells/μL (HR, .94; 95% CI, .77–1.14; $P = .52$), HIV-1 RNA load per 10-fold increase (HR, 1.12; 95% CI, .73–1.73; $P = .60$), hemoglobin level per 1 g/dL (HR, .96; 95% CI, .89–1.04; $P = .33$), and serum sodium level per 10 mmol/L (HR, .86; 95% CI, .66–1.12; $P = .26$) were not predictive of death.

Only 1 death in each arm occurred between 9 and 12 months of follow-up, and 12-month survival results were virtually identical to the those of the primary analysis (HR, 1.12; 95% CI, .81–1.54; *P* = .50).

Adverse Events

There was a high frequency of severe (grade 3 or 4) adverse events in the immediate and deferred ART groups (368 and 318, respectively) (Table 3). Significantly more patients in the immediate ART group experienced grade 4 adverse events (102 vs 87, respectively; *P* = .04). Immediate ART was also associated with a higher frequency of patients with grade 3 and 4 adverse events (109 vs 95, respectively; *P* = .04) and grade 4 adverse events (77 vs 59, respectively; *P* = .03) during the first 2 months.

Thirty-one patients in each group developed a new or recurrent AIDS event; there was no evidence of an association between treatment arm and time to AIDS or death (*P* = .31) (Table 3). Fifty-one (40%) and 50 (40%) patients in the immediate and deferred ART groups, respectively, experienced a neurological event (Table 3); there was no significant association with the treatment arm (*P* = .54) (Table 3). There were no significant differences in laboratory adverse events, although hepatitis occurred more frequently in the immediate ART arm (Table 3).

Secondary Outcome Measures

Secondary outcome measures are summarized in Table 4. The CD4 cell count response at 2 months was higher, and the time to virological suppression was faster, in the immediate ART group. There was no significant difference in CD4 count response at 12 months, and of the 38 patients with documented plasma HIV RNA at 12 months, only 2 (5%, both in the immediate ART group) had a detectable measurement.

DISCUSSION

Currently there is limited evidence to guide the decision when to initiate ART in HIV-infected patients presenting with tuberculosis. Observational studies have suggested that initiation of ART during tuberculosis therapy improves outcome in patients with HIV infection and tuberculosis [14-19]. Clinical trials to determine optimal timing of initiation of ART in HIV and tuberculosis coinfection are currently underway [20], and three randomized controlled trials have reported preliminary data [21, 22]. A South African study of patients with pulmonary tuberculosis has reported a reduction in mortality rate among patients receiving ART during tuberculosis treatment, compared with those who receive ART after completion of tuberculosis treatment [21]. Preliminary data from three studies addressing the optimal time to initiate ART during TB therapy in patients with predominantly pulmonary TB have yielded conflicting results. A Cambodian study [22] showed improved survival among patients randomised to early (2 weeks) versus deferred (8 weeks) ART. In contrast, a South African study [23] and an international study [24] failed to demonstrate a reduction in AIDS and death with early ART, apart from in patients with a baseline CD4 count <50 cells/mm^3. Of note, IRIS occurred more frequently in the early ART arm.

In contrast to these three trials, we found no association between immediate ART and improved survival in patients with HIV-associated TBM; moreover, the confidence interval for the hazard ratio associated with immediate ART treatment was sufficiently narrow to exclude a risk reduction of 20% due to immediate ART. Furthermore, immediate ART appeared to be associated with a higher frequency of severe (grade 4) adverse events, suggesting that early ART initiation may actually be detrimental in this group. It was not possible to determine which component of the ART regimen was responsible for this increase. Interestingly, there was no significant increase in neurological events in the immediate ART group, which might have been anticipated had this excess been caused by efavirenz or a CNS IRIS. Neurological deterioration often occurred suddenly, and it was rarely possible to perform investigations in order to establish the cause. Potential causes include paradoxical reactions (in patients not receiving ART), CNS IRIS, another CNS opportunistic infection, or drug-resistant tuberculosis. Multi-drug-resistant tuberculosis was uncommon in our study, accounting for only 4% of *M. tuberculosis* isolates. One factor that may have attenuated the effects of TBM IRIS on mortality in the immediate ART group was the use of adjunctive corticosteroids; this may have masked excess mortality.

The most common laboratory adverse event was severe hepatitis, defined as a serum transaminase level >5 times the ULN, which occurred in ~20% patients. Although hepatitis appeared to be more common in the immediate ART group, this was not statistically significant. The high rate of hepatitis may have been related to drug toxicities and/or coinfection with HBV and HCV, which was common in the Vietnamese population and more frequent in the immediate ART group. There was no association between treatment group and interruption of antituberculosis or antiretroviral therapy. Severe anemia was also a common adverse event in both groups, but there was no significant difference between groups.

We acknowledge several limitations of our study. The primary endpoint was all-cause mortality at 9 months; we were unable to distinguish deaths related to tuberculosis or HIV infection from other causes of death. Our study included all patients who fulfilled clinical diagnostic criteria for TBM; however, culture confirmation rates were high, and there was no significant difference in outcome between patients who had definite TBM and those who had probable or possible TBM. TBM is the most severe form of tuberculosis, and mortality is associated with disease severity at presentation. If this is compounded by pro-found immunosuppression related to advanced HIV infection, the beneficial effects of ART may not occur quickly enough to alter early TBM-related mortality. As discussed above, preliminary data from three trials involving patients with predominantly pulmonary TB have yielded conflicting results. One Cambodian study suggested was [22]. In contrast, two further studies, also in patients with predominantly pulmonary tuberculosis, have reported preliminary data [23-24]. Both showed no reduction in AIDS or death with immediate ART, apart from in patients with a baseline CD4 count <50 cells/mm^3. Of note IRIS occurred more frequently in the immediate ART arm. Elsewhere, a study of immediate versus deferred ART in HIV-associated cryptococcal meningitis suggests that early ART is detrimental in the setting [25]. Thus, the optimal time to initiate ART in CNS tuberculosis may well differ from that in extracranial tuberculosis. Finally, our study population included

a high proportion of intravenous drug users, who are often coinfected with viral hepatitis; this may limit the generalizability of our findings to other populations.

In summary, our study provides evidence that immediate ART does not improve mortality in patients presenting with HIV-associated TBM. Indeed, the overall mortality among patients with HIV-associated TBM who were treated with ART was surprisingly similar to that among historical patients who did not receive ART during tuberculosis treatment. Immediate ART appeared to be associated with an increase in the frequency of grade 4 adverse events, suggesting that it may be safer to defer initiation of ART in patients presenting with HIV-associated TBM. Our findings emphasize the need for early diagnosis and treatment of HIV infection, before patients present with advanced disease and life threatening opportunistic infections such as TBM.

Acknowledgments

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