ECONOMIC EVALUATION OF INITIAL HAART REGIMEN FOR HIV PATIENTS

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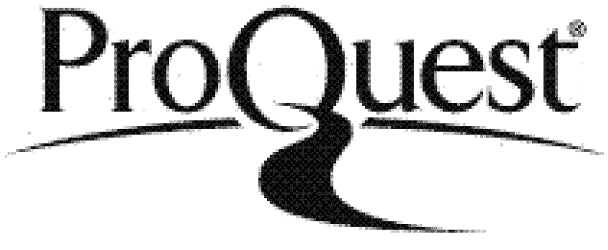

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ABSTRACT

Although 'highly active antiretroviral regimen' (HAART) reduces HIV-related morbidity and mortality, it affects patients and induces HIV viral resistance which could lead to more complex therapeutic regimens. The present study evaluated and compared the cost-effectiveness of a 'protease inhibitor based highly active antiretroviral regimen' (PHAART) with a 'non nucleoside reverse transcriptase inhibitor based highly active antiretroviral regimen' (NHAART) in HIV-patients.

The impact of initial HAART was investigated using retrospective cost analysis over a 10-year period and 6 months prospective HRQoL analysis of 150 patients (male = 125, mean age = 40 years) attending the Cardiff Royal Infirmary and the University Hospital of Wales. Data was collected on each patient's care resource utilization and their health-related quality of life (HRQoL) assessed using the Health Utility Index Mark III (HUI3) questionnaire. The effect of the HAART regimen, demographic attributes and clinical characteristics on costs and HRQoL were analyzed using a multilevel model of change. A Markov Monte Carlo model was then developed to simulate the impact, and evaluate the cost effectiveness, of both regimens beyond the study time horizon.

The mean monthly outpatient cost for all patients was estimated to be £237.59. Patients receiving NHAART as the initial regimen cost significantly more ($p<0.01$, mean = £262.19) than patients receiving PHAART (mean = £234.98). Other factors associated with higher costs were being a non-British national, having a low CD4+ count, a high viral load, and having AIDS. Patients receiving an initial NHAART regimen had a significantly better HRQoL ($p<0.05$). Factors associated with a higher HRQoL included being in employment and being in the asymptomatic stage of HIV. With respect to lifetime cost-effectiveness analysis, PHAART was found to be more cost-effective as an initial regimen since the incremental cost-effectiveness ratio of £8,871 per quality adjusted life years (QALY) gained, was below the UK threshold of £30,000 per QALY.

The findings of this study indicate that patients receiving NHAART as their initial regimen had higher outpatient costs than those initiated on PHAART, but had a better HRQoL. In the long term, however, PHAART was estimated to be more cost-effective than NHAART as an initial regimen for HIV patients.

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ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
AZT	Zidovudine
CEA	Cost-Effectiveness Analysis
CUA	Cost Utility Analysis
d4T	Stavudine
ddc	Zalcitabine
ddI	Didanosine
EFV	Efavirenz
FTC	Emcitrabine
GDP	Gross Domestic Product
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
HUI3	Health Utility Index Mark 3
ICE	Imputation by Chained Equations
ICER	Incremental Cost-Effectiveness Ratio
LPV	Lopinavir
LPV/r	Ritonavir boosted lopinavir
MAR	Missing At Random
MAU	Multi-attribute Utility
MCAR	Missing Completely at Random
MLM	Multilevel Model

MNAR	Missing Not at Random
MOS-HIV	Medical Outcomes Study HIV Health Survey
NFV	Nelfinavir
NHAART	Highly Active Antiretroviral Therapy based on non nucleoside reverse transcriptase inhibitor as third drug
NNRTI	Non nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OECD	Organisation for Economic Co-operation and Development
PCP	Pneumocystis cariini Pneumonia
PHAART	Highly Active Antiretroviral Therapy based on protease inhibitor as third drug
PI	Protease inhibitor
Q-TWiST	Quality-Adjusted Time Without Symptom or Toxicity
QWB	Quality of Well Being
SF-36	Medical Outcomes Study Short Form – 36 Health Survey
SG	Standard Gamble
SQV	Saquinavir
TDF	Tenofovir
TTO	Time Trade Off
UK	United Kingdom
UNAIDS	The Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

GLOSSARY OF TERMS

Benefits	All results or consequences that are of value.
Cost	All resources which have alternative uses.
Cost-effectiveness analysis (CEA)	A type of economic evaluation that compares alternative procedures or programmes in terms of their cost and natural effect or physical unit of consequences.
Cost utility analysis (CUA)	A type of economic evaluation that compares alternative procedures or programmes in terms of their cost and health state preference adjusted consequences.
Cross-sectional data set	A data set collected from a population at a given point in time.
Economic evaluation	The comparative analysis of alternative courses of action in terms of both their costs and consequences.
Economics	The study of how people and society end up choosing with or without the use of money to employ scarce resources to produce various commodities and to distribute them for consumption now and in the future among various groups in society.
Efficiency	Maximum benefit gained from a given resources.
Error term	The variable in a simple or multiple regression equation that contains unobserved factors that affect the dependent variable. The error term may also include measurement errors in the observed dependent or independent variables.
Health Related Quality of Life (HRQoL)	An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations and concerns. It is a broad ranging concept affected in a complex way by a person's physical health, psychological state, level of independence and their relationships to salient features of their environment.
Heteroskedasticity	The variance of the error term, given the explanatory

	variables, is not constant.
Implied values	Values are implied every time a decision is made to do something or not to do something.
Longitudinal data	A data set constructed from repeated cross sections over time.
Multi-attribute Utility (MAU)	Consists of a set of questions and a corresponding set of scores that can be combined into a single index number.
Instrument	The 'instrument' is the questionnaire that asks people to indicate, for each item or health related statement in the questionnaire which response most closely corresponds with their own health. The instrument has multiple attributes if it is a generic instrument that can describe many dimensions of health. It is also a preference instrument if the importance weights attached to each response have been derived using a technique for preference measurement (e.g. time trade-off, standard gamble).
Ordinary Least Square (OLS)	A method for estimating the parameters of a multiple linear regression model. The ordinary least square estimates are obtained by minimizing the sum of squared residuals.
Preference	Umbrella term that describes the overall concept encompassing utility and value. The difference between both types of preference is defined by the outcome certainty in the framed question. A question framed under uncertainty would ask subject to compare two alternatives, where at least on of the alternatives contained uncertainty i.e. probabilities whereas a certain outcome wouldn't. Utility is the type of preference that captured under condition of uncertainty and value is the type that captured under certain condition. An example of utility instrument is standard gamble and example of value instrument is time trade-off.

Quality adjusted life year (QALY)	A metric obtained by multiplying the number of calendar years of life by an index number that reflects the utility of strength of preference for the health state of the person involved. To satisfy the QALY concept, the index must be based on preference, anchored on perfect health and death, and measured on an interval scale.
Sensitivity	Describes an instrument's ability to detect small clinically important changes in an individual's HRQoL.
Specificity	Describes the ability of an instrument to discriminate between a population with a particular disease and a healthy population.
Standard gamble (SG)	A scaling technique considered as gold standard because it employs the axioms of von Neuman and Morgenstern. It consists of a choice between (typically, a life times) in the health state of interest and a gamble between life and death in which the probability of life is varied until the gamble is equally attractive as the certainty of life in the inferior health state. At this point of equivalence, the probability of the favourable outcome is taken as an index of the strength of preference (or utility).
Time Trade-off (TTO)	A scaling technique to derive value based preference weights. In the typical time trade-off, the respondent is offered a choice between the health state of interest for a defined number of years (typically the respondent's life expectancy) and a lesser period of full or normal health. The second option is varied until the respondent indicates that the two options are of equal value. At this point, the preference of the health state may be defined as the ratio of years of full health divided by the large number of years in the health state.
Unbalanced panel	A longitudinal data set where certain years or periods of data are missing for some cross-sectional unit.

CHAPTER 1

General Introduction

BACKGROUND

The manifestation of Human Immunodeficiency Virus (HIV) infection in humans was first described in 1981 when five homosexual men with a history of cytomegalovirus and candida mucosa infection were treated for biopsy-confirmed *Pneumocystis cariini* pneumonia in California (Centre for Disease Control and Prevention, 1981). Two of them died during treatment. It was not until 1982 that the first link between the infection and blood was made by the Centre for Disease Control. The pathogen responsible was later termed HIV. Prior to 1996, the disease was highly fatal since patients were often diagnosed at an advanced stage of infection (Samet et al., 2001). Patients without AIDS had an annual mortality rate of 2% whilst 50% of patients with AIDS died within six months of diagnosis.

1996 marked the most important milestone in HIV history with the success of Highly Active Antiretroviral Treatment (HAART) as reported at the 12th Vancouver AIDS Conference. HAART, a treatment strategy describing anti-HIV therapy with three or more drugs has been proven to be very effective in slowing the progression to AIDS, resulting in lower mortality and higher survival rates (Moore and Chaisson, 1999).

There are currently more than 25 antiretroviral drugs on the market for HIV infection in four different pharmacological classes (protease inhibitors, non nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, and fusion inhibitor) (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006). HAART was typically recommended to comprise of at least two nucleoside reverse transcriptase inhibitor (NRTI) drugs that formed the backbone of the regimen. The third drug could again be from any

class but most guidelines (Hammer et al., 2006, British HIV Association, 2005, European AIDS Clinical Society, 2005) have recommended HAART based on 'non nucleoside reverse transcriptase inhibitor' (NNRTI) efavirenz, as the third drug (from hereon, HAART based on NNRTI will be abbreviated as NHAART) or a third drug from protease inhibitor (PI), ritonavir boosted lopinavir (from hereon, HAART based on PI will be abbreviated as PHAART) as the first line choice for treating the antiretroviral-naïve HIV patient.

Because of interactions between drugs, additive toxicity (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006) and cross-resistance (Bangsberg et al., 2006) that could limit and lower viral response in subsequent treatment, the best possible initial regimen needs to be selected. There is however a considerable lack of long term clinical evidence on HAART. This is a result of limited experience with the new drugs and the expedited approval process of HIV drugs that rely on surrogate markers i.e. HIV viral load suppression and CD4+ count improvement instead of final outcome.

Although there is no large head-to-head randomized clinical trial comparing these two regimens, current evidence found that NHAART was more efficacious in suppressing HIV than PHAART. In two recent exploratory studies (Manfredi et al., 2004, Domingo et al., 2006) and one small clinical trial (Riddler et al., 2006), it was demonstrated that NHAART with efavirenz (EFV) achieved a higher proportion of patients with a suppressed viral load at week 96 than patients who received PHAART with ritonavir boosted lopinavir (LPV/r) (Riddler et al., 2006). PHAART however showed a better

immunological outcome in terms of CD4+ count improvement. Whether this improvement will translate into a better long term clinical outcome is unknown. The major disadvantage of PHAART are the metabolic and gastrointestinal complications that often result in disfigurement (Behrens et al., 2000). Although NHAART does not pose these risks, patients receiving them are at risk of skin and long term neuropsychiatric adverse effects (Lochet et al., 2003).

PHAART's ADRs were perceived to have more treatment limiting effects than NHAART and thus less favoured in the UK (Gazzard et al., 2006). The most recent UK guidelines also recommended NHAART as the first line initial regimen instead of either PHAART or NHAART as was previously recommended (Gazzard et al., 2006).

It is important to note however that the recommendations made by the guidelines were based on results from only three years of HAART intervention on HIV surrogate markers. Although these markers demonstrated good prognostic properties of patients survival and progression (Mellors et al., 1997), they are not a replacement for long term health outcomes. This is particularly true in patients with longer survival rates, since they are exposed to increased risk of adverse drug reactions and treatment changes that could affect their overall quality of life and care. It is clear therefore that the choice of an initial HAART regimen involves many variables that need to be balanced out carefully considering the impact it could make on patients' health outcomes.

HEALTH ECONOMICS FRAMEWORK

Economic analysis, part of a larger health economics discipline, is increasingly used in the medical field today. A quick Medline search would retrieve 7,000 economic articles published in the early 1980's increasing to 20,000 in 2006. Globally, economic analysis is formally required in many countries for pharmaceutical reimbursement (Australia) or for technology appraisal (England and Wales).

These trends reflect modern recognition of rational decision making in light of increased health care costs compared with available resources. Among OECD countries including the UK (excluding Finland), health spending had outgrown Gross Domestic Product (GDP) from 7% in 1990 to 8.8% in 2004 (OECD, 2006). Most of this (73%) was publicly funded through taxes.

Economics is defined as 'the study of how people and society end up choosing with or without the use of money to employ scarce resources to produce various commodities and to distribute them for consumption now and in the future among various groups in society' (Samuelson and Nordhaus, 2000).

There are two concepts that play an important role in economics. Firstly the concept of resource scarcity that stems from the understanding that resources are finite compared to infinite wants and needs. This consequently implies that not all wants and needs can be fulfilled at once, and certain trade-offs need to be made which result in the second economic concept of opportunity cost. This is the benefit that must be given up as a result of the decision.

Addressing an issue from an economic perspective is simply trying to explicitly and systematically evaluate the choices in-hand and determining the

right balance of cost and benefit. The general steps involved include defining programs, estimating program resources and benefits, identifying margins and setting up priorities (Green, 2003). Throughout these, four basic concepts of economics come into play i.e. effectiveness, efficiency, economy and equity. Effectiveness refers to the degree to which an objective is attained by the application of a bundle of resources (Green, 1990). Efficiency is an economic term that deals with the relation of input to output. It seeks to maximize benefit gained from given resources. Equity can roughly be defined as justice and fairness. It deals with the question of how much good can be done with whatever resources are available while at the same time, ensuring patients with the same need receive equal treatment (Mooney, 2003). These are used in parallel and mutually support each other in the decision making process.

Health economics is concerned with the allocation of health and health care in the face of scarcity. The traditional theoretical base of such allocation is societal welfare defined as an aggregation of utility across all individuals. According to this theory, resources should be allocated to maximize welfare. In the absence of a perfectly competitive market in health care, economic evaluation techniques can be used to mimic market allocation for welfare maximization (Drummond and McGuire, 2001).

WHY THE CHOICE OF INITIAL HAART COMBINATION REQUIRES AN ECONOMIC PERSPECTIVE?

Much progress had been made in terms of our understanding of the pathogenesis, and virology that leads to improved management of HIV

infection. This progress together with the other factors described below, provides an impetus for adopting an economic perspective in analyzing issues on the appropriate HAART combination selection.

Increasing Complexities in Management of HIV Infection

HAART treatment not only affects antiretroviral drug procurement cost, but also other resources e.g. adverse drug reaction monitoring and treatment, laboratory monitoring, health professional time, hospital bed occupancy and palliative care support (Beck et al., 1998a). Some of these areas may see an increase whilst some may see a saving from the treatment.

Advances of knowledge in new adverse drug reaction mechanisms, and virology have increased and complicated routine monitoring regimes for HIV patients that now include a multitude of laboratory tests and imaging. The tests are usually taken at routine clinic visits every three to six months but are more frequent and extensive for patients on treatment (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006) (Table 1.1).

Besides physical examinations, patients with HIV are also routinely tested for surrogate markers such as CD4+ count, lymphocyte and viral load. This is taken to monitor disease progression and treatment effectiveness.

From time to time, biochemistry, and haematological indices are taken. This is essentially to monitor any laboratory abnormalities that occur as a result of the HIV progression and also the multiple adverse drug reaction that could occur with HAART administration. In addition, patients with HIV usually present with other sexually transmitted diseases and the pharmacokinetics of the drug

itself could adversely affect patients with this co-morbidity e.g. hepatitis B. For this reason too, it is common practice to monitor patients for other sexually transmitted diseases as well.

Table 1.1 Routine tests and examinations in HIV patient

TEST	NEWLY DIAGNOSED PATIENT	UNTREATED PATIENT	TREATED PATIENT
HIV viral load	\	2 – 4 times per year	After treatment initiation, at months, 1 and 3, then 4 times per year
CD4 cell count	\	2 – 4 times per year	4 times per year
Complete blood cout	\	2 – 4 times per year	4 times per year
Biochemical profile including CPK, liver and renal function	\		4 times per year
Lipid profile	\		4 times per year
Glucose	\		4 times per year
Serology: Hepatitis A Virus, Hepatitis B Virus surface antigen, core antibody, Hepatitis C Virus, Venereal Disease Research Laboratory, Treponema palladium haemagglutination assay (TPHA), toxoplasmosis, cytomegalovirus (IgG)	\	Re-test yearly if negative at outset	Re-test yearly if negative at outset
Chest X-ray	\ As baseline		
Dilated fundoscopy	If CD4 < 100	2 – 4 times per year if CD4<100	2 – 4 times per year if CD4<100

The extensive evidence (Albrecht, 2000, Aleman et al., 2002, Brenner et al., 2000, Burkle, 2002) regarding the development of HIV resistance towards antiretroviral agents has prompt experts (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006, Gazzard et al., 2006) to recommend routine genotypic resistance testing before patient initiated antiretroviral treatment, and before switching antiretroviral treatment.

Changes in the Natural History of HIV Infection

With new management regimes for HIV, particularly Highly Active Antiretroviral Therapy (HAART), mortality rates were significantly reduced which subsequently transformed the disease facet to a chronic stage disease (Fenton and Valdiserri, 2006) (Figure 1.1). In fact, it was estimated that the mortality rate continued to decline from 2% between 1998 – 2000 to 1% in 2001 – 2003 (Sabin et al., 2006). This was attributed to the longer median incubation time of HIV in the latency period, from 10 to 21 – 23 years (Artzrouni, 2004).

Rising Pandemic

Globally there are increasing numbers of people living with HIV and dying from AIDS (UNAIDS/WHO, 2006). The global HIV prevalence in 2006 was estimated at 39.5 million, with an incidence of 4.3 million newly diagnosed and a mortality rate of 2.9 million people. This represents an increase of more than 7% over cases recorded at the end of 2004. The most rapid increases were observed in East Asia, Central Asia and Eastern Europe where the number of people living with HIV in 2006 was 21% higher than that estimated in 2004. Sub-Saharan Africa was still the most affected region with two-third of worlds HIV cases lives there. In UK, the prevalence of HIV diagnosis in adults by the end of 2005 was 63,500 with annual incidence of 3.2% (The UK Collaborative Group for HIV and STI Surveillance, 2006) (Figure 1.2). There was a stark increase in the diagnosis and deaths from HIV/AIDS since the first case were recorded in 1981.

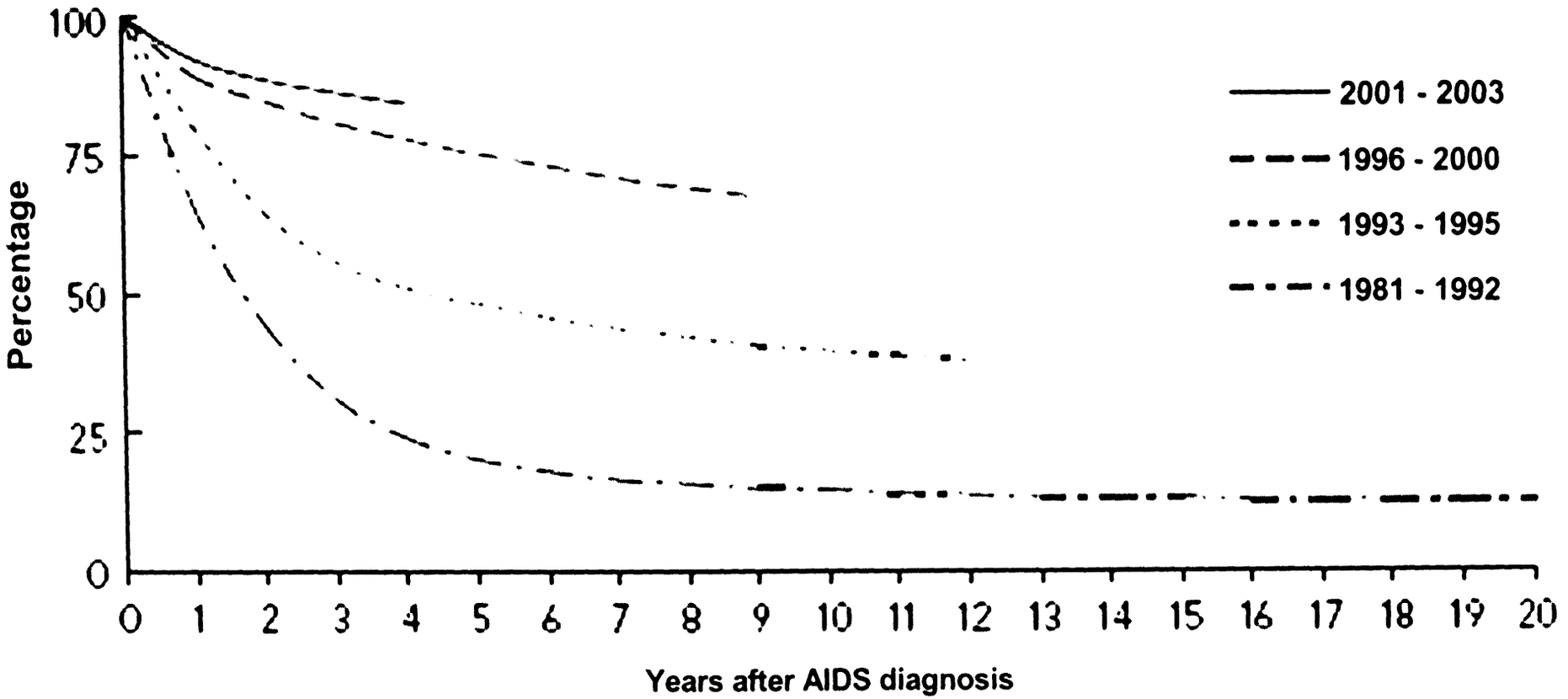


Figure 1.1 Percentage of persons surviving through June 2005, by years after AIDS diagnosis cohorts during 1981 – 2003 and by year of diagnosis – United States. Source: Fenton and Valdiserri (2006)

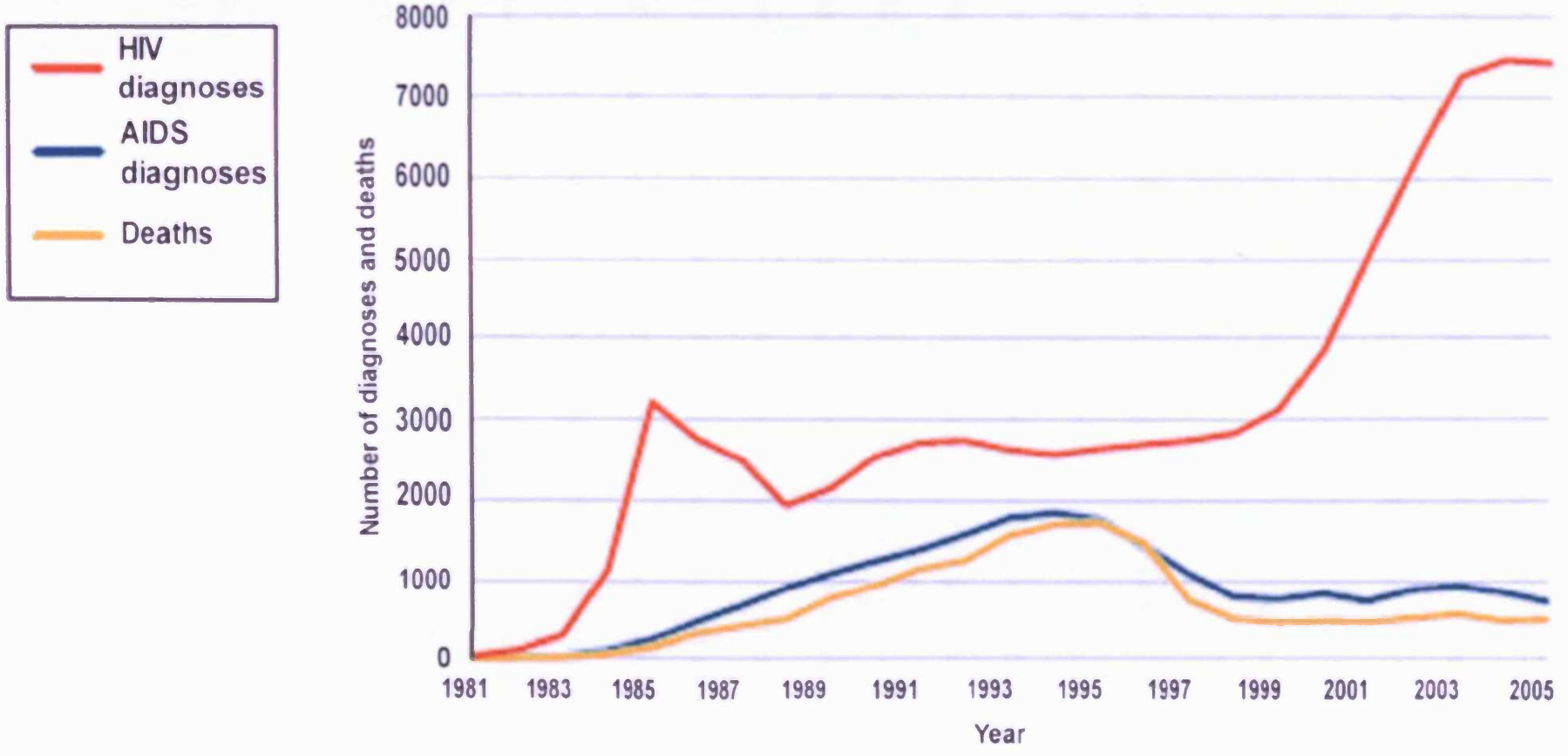


Figure 1.2 HIV and AIDS diagnoses and deaths in HIV-infected people, United Kingdom 1981 to 2005. Source: Health Protection Agency (2004)

Resource Limitation

The advancement in HIV management had a profound impact on the total health care cost. Domestic spending for this disease increased significantly in many countries including the poorest but was still short of the required amount to effectively manage the disease. UNAIDS estimated that at least US$10 billions were needed in 2005 to combat the disease and this would need to increase to US$16 billions by 2007 (UNAIDS/WHO, 2003).

Given the potential difference the choice of initial HAART combination would make on patients' long term clinical and quality of life, there must also be a significant impact on health care resource allocation. In an ideal world where resources are unlimited, the health care system would be able to accommodate this impact – caring for a non-responsive patient with salvage treatment, while treating any newly diagnosed patients. Unfortunately, the real world has scarce health care resources that force many health care decision-makers to make prudent choices.

In short, technological advancement and epidemiology changes have increased the demand for health care. In view of resource scarcity, a rational choice has to be made for an initial HAART regimen combination that maximizes health outcomes for HIV patients. This can be done by evaluating both costs and benefits of the choice at hand. In order to grasp these, a literature review on the effect of HAART on cost and quality of life of HIV patients was conducted.

LITERATURE REVIEW OF HAART EFFECT ON ECONOMIC AND HUMANISTIC OUTCOMES

Literature Retrieval

Literature was retrieved through: electronic secondary literature; reference lists; and a manual search of selected journals. The search of electronic sources and catalogues was conducted using an established literature search strategy (Centre for Evidence-Based Pharmacotherapy, 2001) with a few modifications to search for economic and quality of life studies in HAART-based antiretroviral treatment. The following keywords were used in the search:

exp.cost-benefit analysis/; exp cost and cost analysis/; exp economics, medical/; exp economics, hospital/; exp technology assessment, biomedical/; exp cost$.mp/; exp quality of life/; exp utility/; exp economic evaluation$.mp/; MeSH (HIV infection, anti-HIV agents) and then select 'economics' under the disease-specific tree.

(exp = explode; OVID Medline search term that allows to include more specific terms indexed under to the broad keyword)

Database built-in expansion facilities and Boolean operators – AND, OR, and NOT were used variably and consistently between each term to broaden and narrow the references found. Database and electronic catalogues used were Medline, BIDS-Embase, and The Cochrane Library. Journals selected for manual search were those with a known reputation in the pharmacoeconomic and HIV field i.e. Pharmacoeconomics, AIDS, HIV Medicine and International Journal of STD and AIDS.

Only original English language articles were retrieved because of the language barrier. It is important to note that HAART regimen only reached its consensus in 1996 following the 12th Vancouver AIDS Conference. Therefore, articles selected for review were from 1996 onwards to capture articles pertaining to HAART regimen evaluation only. Retrieved articles were further filtered out for studies that did not use HAART as a routine for patients, or did not provide enough details for

meaningful comparisons by explicitly describing study period, location, population, data sources, methods to elicit cost, and methods to elicit quality of life. Due to differences in the standard of HIV care, retrieval was restricted only to developed countries (Japan, US, Australia, New Zealand, and Western Europe).

For review of cost analysis study, only articles that used a bottom up costing approach were selected. For the review of quality of life studies, observing aims and objectives of the present study, only preference based quality of life research papers were selected. This would exclude studies that used psychometric tools e.g. SF-36 and MOS-HIV. For the review of economic evaluation of HAART treatment, studies that focused on anything other than primary antiretroviral care such as prevention evaluation were excluded.

All costs reviewed were converted and inflated to 2005 UK£ using a gross domestic product inflator (Lawrence and Williamson, 2006).

Review of cost analysis in HAART era

All cost analysis studies reviewed came from three countries – France (Yazdanpanah et al., 2002, Flori and le Vaillant, 2004), United Kingdom (Beck et al., 1998c), and United States of America (US) (Gebo et al., 1999, Bozzette et al., 2001, Chen et al., 2006) with the US making the biggest contributions (Table 1.2). None of the studies however reported comparisons between different combinations of HAART.

Analysis of antiretroviral effect mostly focuses on the temporal effect of introduction of HAART on the total costs. Such studies have concluded that there was a significant effect of HAART on the total cost, with estimates from 28% (Beck et al., 1998c) to 56% (Chen et al., 2006) of the total cost.

There was also a decrease in in-patient costs observed up to one third at end of the three year observation period (Flori and le Vaillant, 2004). The decrease of in-patients cost however was accompanied by an increase in outpatient and drug cost. Other studies found a more moderate decrease in in-patient cost (Gebo et al., 1999) but there was a general agreement on the direction of the change. Gebo et al (1999) however found that although hospitalization rates decreased in patients receiving HAART, the total cost itself did not decrease.

Bozzette et al (2001) also found that the people in disadvantaged groups (women, public health insurance, blacks and low education) in the US had less outpatient utilization than in-patient care. This highlights the issue of access to care among certain groups even in a developed country.

Cost also differed significantly in relation to HIV severity which was investigated through surrogate markers and HIV clinical stages stratification. Patients in the AIDS stage incurred up to three times health care costs compared with the less advanced symptomatic patients (Beck et al., 1998c). The cost of acute specific ADE was higher and was estimated to double the cost of patients in the chronic AIDS stage (Yazdanpanah, 2004). There was a discrepancy between the two estimates which could be attributed to the inclusion of medication costs in the latter study.

Most of these studies however were not conclusive as to causality and were limited in their application. This was because the authors analyzed the change by aggregating the cost of stratified patients at different cross-sectional times, rather than actually following up patients individually through time. The studies also lack information and details on the combination of HAART used in the settings. This could jeopardize the results, as HAART with larger numbers of combinations or newer drugs would incur higher costs.

Table 1.2 Hospital costs of treating adult HIV patients in developed countries

STUDY & PERIOD	COUNTRY	RESOURCE SOURCE & TYPE	COST PER PATIENT PER MONTH (2005 UK£)				
Beck (1998)	UK	Source: HIV clinic database (5708 patients); Type: Inpatient, outpatient		Asymptomatic	£356.93		
				Symptomatic	£593.09		
				AIDS	£1,599.11		
Gebo (1999) 1995 - 1997	US	Source: Administrative database (695 patients); Type: Inpatient, outpatient clinic, medications (antiretroviral, inpatient antiinfective) community care, emergency care			CD4<50	50 - 200	201 - 500
			1995	Inpatient	£951.74	£432.61	£450.21
				Outpatient	£280.10	£161.31	£173.04
				Pharmacy	£486.87	£195.04	£120.98
				Community care	£189.17	£46.93	£16.13
				Emergency room	£19.80	£23.46	£30.06
			1996	Inpatient	£726.57	£491.27	£322.62
				Outpatient	£262.50	£184.78	£172.31
				Pharmacy	£470.00	£372.48	£230.24
				Community care	£60.86	£45.46	£14.66
				Emergency room	£27.13	£31.53	£30.06
			1997	Inpatient	£817.56	£307.96	£354.15
				Outpatient	£351.95	£172.31	£226.57
				Pharmacy	£494.20	£230.24	£327.76
				Community care	£206.77	£14.66	£27.13
				Emergency room	£24.93	£30.06	£21.26
Bozzette (2001) 1996 - 1998	US	Source: Patient questionnaire (2864 patients); Type: Inpatient, outpatient, medications (antiretroviral, other)		CD4 >500	£412.93		
				200 - 499	£717.91		
				50 - 199	£712.94		
				<50	£1,819.75		
				Asymptomatic	£828.57		
				Symptomatic	£868.38		
				AIDS	£1,371.73		

Table 1.2 Hospital costs of treating adult HIV patients in developed countries (cont.)

STUDY & PERIOD	COUNTRY	RESOURCE SOURCE & TYPE	COST PER PATIENT PER MONTH (2005 UK£)				
Yazdanpanah (2002) 1994 - 1998	France	Source: Clinic database (1232 patients); Type: Inpatient (personnel, laboratory, procedures). Outpatient (personnel, laboratory, procedures). Medication (antiretroviral, prophylaxis)	No AIDS	CD4>500	£698.93		
				301-500	£823.36		
				201-300	£905.27		
				101-200	£1,016.20		
				51-100	£910.70		
				<50	£957.24		
			Specific ADE		£2,612.64		
			History of ADE		£1,359.15		
			Death		£10,095.29		
Flori (2004) 1995 - 2000	France	Source: Clinic database (30 French hospital;2203 patients); Type: Inpatient, outpatient, medication (ARV)	1995	Inpatient	£400.38		
				Outpatient	£241.39		
				ARV	£76.00		
			1998	Inpatient	£105.95		
				Outpatient	£213.76		
				ARV	£304.35		
			2000	Inpatient	£102.36		
				Outpatient	£184.14		
				ARV	£253.17		
Chen (2006) 2000 - 2001	US	Source: Administrative database (635 patients); Type: Inpatient, outpatient, medication (antiretroviral, anitbiotics)		Total	Inpatient	Outpatient	ARV
			<50	£2,054.10	£469.67	£137.31	£610.35
			50-199	£1,341.81	£189.43	£109.53	£666.97
			200-349	£1,027.50	£66.69	£95.64	£671.08
			>350	£780.72	£79.17	£68.88	£528.93
			All	£1,048.08	£131.69	£87.60	£590.39

Review of quality of life in HAART era

There are two commonly used methods to elicit humanistic outcomes of health status: the descriptive method; and the preference method (Drummond et al., 1997). The descriptive method is grounded in psychometric theory that seeks to discriminate among levels of health status (presence, frequency, intensity) by providing numerical assessments of individuals' health status (Richardson et al., 1998). Examples of such instruments are the SF-36, MOS-HIV and the UKSIP. However, these measures do not essentially reflect the value that patients in the general population place on the health attributes measured. For example, the loss of an arm for two individuals might result in the same numerical ranking on a psychometric scale but conversely might value that health state very differently. This limits application in general comparisons and economic evaluations.

The preference method is based on the traditional economic von Neumann-Morgenstern utility theory that describes a normative model of rational decision-making under conditions of uncertainty (Drummond et al., 1997). A decision-making question framed under uncertainty would compel the subject to compare alternatives, where at least one contained uncertainty in the form of probabilities. This restriction however was loosened to accommodate other preference elicitation techniques that measured under conditions of certainty (i.e. no unknown or probabilities) such as rating scales, or time trade-off.

In general terms, the preference method describes the desirability of a set of outcomes (Drummond et al., 1997). There are two approaches to measuring preference (Richardson et al., 1998). The first is by direct elicitation using standard gamble (SG), time trade-off (TTO) or rating scale (RS).

Table 1.3 Health related quality of life weight for adult HIV patients

STUDY	HEALTH STATE	QOL WEIGHT	ASSESSMENT INSTRUMENT	SUBJECT
Mathews and May (2007) US	CD4<50	0.645	EuroQoL (EQ-5D) VAS	956
	CD4 50-199	0.700		
	CD4>200	0.750		
	VL>1000	0.700		
	VL<1000	0.755		
Wu (2002) US	No OI	0.712	EuroQoL (EQ-5D) VAS	990
	After OI	0.602		
Harris (2002)	KS Cutaneous	0.270	Time Trade Off (TTO)	17
	KS Systemic	0.070		
	Treated	0.310 - 0.550		
	KS Cutaneous	0.110	Rating Scale (RS)	
	KS Systemic	-0.100		
	Treated	0.380 - 0.440		
Delate (2001) US	CD4<200	0.570	EuroQoL (EQ-5D)	242
	CD4>200	0.650		
	VL<30,000	0.650		
	VL>30,000	0.540		
	CD4<200	0.625	EuroQoL (EQ-5D) VAS	
	CD4>200	0.708		
	VL<30,000	0.696		
	VL>30,000	0.596		
Bayoumi (1999) Canada , US	symptomatic	0.800	Standard Gamble (SG)	76
	minor ADI	0.650		
	major ADI	0.410		
	symptomatic	0.810	Time Trade Off (TTO)	
	minor ADI	0.650		
	major ADI	0.440		
	symptomatic	0.700	Visual Analogue (VA)	
	minor ADI	0.460		
	major ADI	0.250		
	symptomatic	0.810	Health Utility Index Mark 2 (HUI2)	
	minor ADI	0.740		
	major ADI	0.690		
	asymptomatic	0.900		

Abbreviation: VL = viral load, ADI = AIDS defining illness, KS = Kaposi sarcoma, VAS = visual analogue scale, VA = visual analogue, OI = opportunistic illness

The second approach is by indirectly measuring this preference through applying an external tariff of previously direct elicitation of population preferences on patient ratings of his or her health status. Examples of instruments using this approach are the Health Utility Index, EuroQoL, and Quality of Well Being.

The literature reviewed on the quality of life of HIV patients was restricted to studies that used preference-based methods. Most of the studies retrieved used psychometric-based instruments. Only five studies used preference-based instruments and met the review criteria (Mathews and May, 2007, Wu et al., 2002, Harris et al., 2002, Delate and Coons, 2001, Bayoumi and Redelmeier, 1999) (Table 1.3).

Most of the studies were from the US and used the EuroQoL as the health related quality of life (HRQoL) measurement instrument. The HRQoL weight varied between instruments and across all studies even with the same instrument. The direction of change however was approximately similar though the magnitude was not comparable. This demonstrates a contentious issue in the field of HRQoL whereby the variation brings to the fore the question of generalisability to other populations.

The studies reviewed also did not assess the impact of antiretroviral treatment, specifically HAART on HRQoL. Most studies focused on HRQoL measurement stratified by disease severity which was defined either by HIV clinical stage (Bayoumi and Redelmeier, 1999), or by the use of a surrogate marker, CD4+ count and viral load (Delate and Coons, 2001, Mathews and May, 2007). All of these found that HRQoL decreased with increased HIV severity. A few studies focused on 'acute AIDS defining event' (ADE). Harris (2002) assessed the HRQoL in patients with Kaposi's sarcoma comparing the less benign cutaneous form of Kaposi's sarcoma with the more severe systemic Kaposi's sarcoma. Patients' quality of life

was severely decreased in patients with acute Kaposi's sarcoma with a systemic HRQoL weight of 0.07 using TTO and -0.10 using RS. The HRQoL was higher in the cutaneous form with estimates of 0.27 and 0.11 using TTO and RS respectively. The HRQoL score of Kaposi's sarcoma in Harris (2002) was far lower than estimated by Wu (2002) in patients with ADE. However, it should be noted that Wu (2002) focused on different ADE (i.e. cytomegalovirus infection). This however suggested that different ADE would have different HRQoL.

Review of Economic Evaluation in the HAART era

For a physician prescribing treatment for a treatment naïve patient in this HAART era, or for decision makers that are to decide which treatment should be funded, the question is, what is the treatment combination that would give the most value for money? What combination would have better survival, humanistic and economic outcomes? With longer survival, but more complex management, how does the cost change? Or specifically, does longer survival equate to better quality of life for patients?

In the plethora of highly sophisticated disease management research, physicians, and policy makers alike not only find themselves challenged to put efficacy evidence integration into practice, but also to balance the books against economic and humanistic impacts in deciding the best treatment.

Rather than leave the decision to fate or gut feeling, the science of decision-making has evolved to aid in the decision-making process through employment of cross discipline tools including economics, education and psychology. The current review aimed to gather information on the efficiency of HAART especially between different regimen combinations.

Economic evaluation tools that are commonly used to evaluate the technical efficiency, or benefit maximization of a fixed resource are cost-effectiveness analysis (CEA) and cost utility analysis (CUA). Both tools evaluate choices in term of cost and non monetary benefit. The difference is that CEA evaluates benefits in its natural unit (e.g. life expectancy) while the benefit evaluated in CUA is a utility weighted life expectancy (QALY). Some text books (Gold et al., 1996) consider CUA as a sub set of CEA.

For consistency purpose and ease of discussion, the categorization by Drummond (1997) that separates these tools was applied in this thesis. This efficiency estimate is usually given in an incremental cost effectiveness ratio (ICER) that shows the 'additional costs that one service or programme imposes over another, compared with the additional effects, benefits, or utilities it delivers' (Drummond et al., 1997). ICER is usually expressed as either cost per life years gained (£/LY gained) or cost per quality adjusted life years gained (£/QALY gained). The results could show that the comparator is less costly but more effective than the baseline (dominate) or the baseline to be less costly and more effective than the comparator (dominant) in which case the conclusion is clear i.e. alternatives that are less costly and more effective are the most cost-effective (Briggs et al., 2002). Most often, however, the comparator is more costly and effective than the baseline. One way to interpret this ICER is by comparing it to other economic evaluation results currently in service as an implied threshold of cost-effectiveness. The value often quoted is the ICER of hospital haemodialysis at £25,000 per gained benefit. Values below this threshold are deemed to demonstrate the cost-effectiveness of the comparator.

Table 1.4 Summary of studies reporting economic evaluation of HAART treatment

Reference	Compared Intervention	Perspective	Method	Cost measure	Effectiveness measure	Lifetime Results	
Moore, 1996	(IDV+ 3TC + AZT) vs AZT	Payer	CEA, Markov cohort simulation model	Healthcare cost (administrative database)	Survival RCT and observational-based (Chaisson et al 1995, O'Brien et al 1996)	ICER	£6864/LY
Messori, 1997	(SQV + AZT + ddc) vs AZT	Societal	CEA, survival analysis	Expenditure of healthcare resource only.	Survival RCT-based, extrapolated utility Q-TWIST	ICER ICER2	£20591/LY £32336/QALY
Cook, 1999	(IDV + 3TC + AZT) vs (3TC + AZT)	Payer (societal according to author)	CEA, Markov Monte Carlo simulation model	Healthcare costs (administrative database), additional laboratory test (HIV RNA test), medication (ARTV)	Survival RCT-based.	ICER1 ICER2	Dominate £9294/LY
Sendi, 1999	HAART vs NART	Payer and societal	CEA, Markov Monte Carlo simulation model	Medication (Swiss HIV Cohort Study), health care cost and productivity cost.	Survival observational based	ICER1 (payer) ICER2 (societal)	£14619/LY Dominant
Trueman, 2000	(ABC + AZT + 3TC) vs (AZT + 3TC)	Payer	CUA, CEA Markov cohort simulation	Inpatient cost, medications (antiretroviral and anti-infectives), diagnostic tests, from NPMS-HCC and community costs.	1. Survival RCT and observational-based. Triple therapy relative risk estimated from dual therapy trial. 2. HRQoL from external HUI utilities estimates.	ICER1 ICER2	£9899/LY £12056/QALY

Key: NART = No Antiretroviral Therapy, 3TC = Lamivudine, ABC = Abacavir, AZT = Zidovudine, ddI = didanosine, ddC = Zalcitabine, d4T = Stavudine, IDV = Indinavir, ICER = Incremental Cost-Effectiveness Ratio, NA = Not Available, ILY = Incremental Survival, NPMS-HHC = National Prospective Monitoring System – HIV Health Economics Consortium

Table 1.4 Summary of studies reporting economic evaluation of HAART treatment (Cont 1)

Reference	Compared Intervention	Perspective	Method	Cost measure	Effectiveness measure	Lifetime Results	
Anis, 2000	1. (2NRTI + 1PI@1NNRTI) vs (AZT + ddC@ddI) 2. (2NRTI + 1PI@1NNRTI) vs d4T + (ddI@ddC) @ (3TC + (AZT@ddI@ddC@d4T))	Payer	CEA, survival analysis	Inpatient costs, procedures, investigations, physicians incurred in St Paul's Hospital.	Survival observational based	Payer Societal	£17093/LY £22797/QALY
Freedberg, 2001	HAART vs no ART	Societal	CUA. Markov Monte Carlo simulation	Direct cost for acute illness and routine medical care (ACSUS), laboratory cost (CD4, HIV RNA test), medication (ARV)	Survival RCT and observational-based and HRQOL from ACTG RCTs' questionnaire (study not stated) converted to utility by Torrance's method	CD4>500 CD4<50 ICER	£57,969 £44,350 £8790 - 15552/QALY
Miners, 2001	HAART (2NRTI + PI/NNRTI) vs 2NRTI	Payer	CUA. Markov Monte Carlo simulation	Inpatient, outpatient, medication (Clinical database)	1. Survival observational based 2. HUI2 HRQOL	HAART Dual NRTI ICER1 ICER2	£119,190 £77,135 £25865/LY £31349/QALY

Key: HAART = Highly Active Antiretroviral Therapy, NART = No Antiretroviral Therapy, PI = Protease Inhibitor, NNRTI = Non Nucleoside Reverse Trascriptase Inhibitor, NRTI = Nucleoside Transcriptase Inhibitor, 3TC = Lamivudine, ABC = Abacavir, AZT = Zidovudine, ddI = didanosine, ddC = Zalcitabine, d4T = Stavudine, IDV = Indinavir, LY = Life Year, QALY = Quality Adjusted Life per Year, RCT = Randomized Controlled Trial, ICER = Incremental Cost-Effectiveness Ratio, NA = Not Available, ILY = Incrementeal Survival and, @ = or.

Table 1.4 Summary of studies reporting economic evaluation of HAART treatment (cont 2)

Reference	Compared Intervention	Perspective	Method	Cost measure	Effectiveness measure	Lifetime Results
Caro, 2001	(EFV + AZT + 3TC) vs (IDV + AZT + 3TC)	Payer	CEA, Markov's Monte Carlo simulation	Acute inpatient care (administrative database), subacute inpatient, home healthcare, hospice and outpatient (ACSUS), physician and laboratory costs and medication (antiretroviral)	Initial regimen and subsequent treatment failure response was clinical trial and observational based.	Not presented but EFV based regimen was dominant for the first five years
Simpson, 2004	(LPV/r + d4T + 3TC) vs (NFV + d4T + 3TC)	Payer	CUA, Markov cohort simulation model	Cost categorized into routine care, treatment switch, cost of OI care (administrative database), medication (ARV). ARV regimen 2nd line given as average ($50.50) and 3rd line ($58.00).	Efficacy derived from clinical trials, HRQoL from transformed psychometric survey	LPV/r £18,221,039 NFV £18,036,552 ILY 25 ICER1 £4073/LY ICER2 £4250/QALY

Key: HAART = Highly Active Antiretroviral Therapy, NART = No Antiretroviral Therapy, PI = Protease Inhibitor, NNRTI = Non Nucleoside Reverse Trascriptase Inhibitor, NRTI = Nucleoside Transcriptase Inhibitor, 3TC = Lamivudine, ABC = Abacavir, AZT = Zidovudine, ddI = Didanosine, ddC = Zalcitabine, d4T = Stavudine, IDV = Indinavir, LY = Life Year, QALY = Quality Adjusted Life per Year, RCT = Randomized Controlled Trial, ICER = Incremental Cost-Effectiveness Ratio, NA = Not Available, ILY = Incremental Survival and, @ = or.

Past economic evaluations of the HAART regimen can generally be divided into two broad groups based on the stated or deduced objectives (Table 1.4). The first group consists of studies evaluating HAART against no antiretroviral, monotherapy or dual therapy. Most of these studies were published in the early HAART period (prior to 2000) and aimed to position the newly available HAART as the treatment of choice compared to the previous standard of monotherapy or dual therapy treatment.

In the first group, several incremental cost-effectiveness ratio (ICER) conclusions on HAART in comparison to no antiretroviral therapy, monotherapy and dual therapy were drawn. HAART was estimated to be more cost-effective than no therapy (ICER: £14,619/LY gained and £8,790 – £15,552/QALY gained) (Freedberg et al., 2001, Sendi et al., 1999). HAART was also more cost-effective than monotherapy (ICER: £6,864 - £20,591/LY gained and £32,336/QALY gained) (Cook et al., 1999, Moore and Bartlett, 1996, Messori et al., 1997, Trueman et al., 2000, Freedberg et al., 1999). When compared to dual therapy, HAART was still cost-effective with ICER of £9,294 - £25,865/LY gained and £12,056 - £31,349/QALY gained (Risebrough et al., 2000, Risebrough et al., 1999, Miners et al., 2001b, Anis et al., 2000, Freedberg et al., 1999, Trueman et al., 2000, Cook et al., 1999).

The second group consists of studies evaluating the efficiency of the different combination of HAART treatment itself. There are only two studies in this group to date. Caro (2001) has compared NHAART based on EFV to PHAART based on indinavir (IDV) in a fixed combination with lamivudine (3TC) and zidovudine (AZT). The study concluded that the EFV based regimen is dominant i.e. less costly and more effective than IDV. They however assumed that the salvage treatment regimen was the same for both initial regimens in the analysis. Although this would help to isolate the effect of the third drug when other salvage treatment was assumed the

same, regardless of initial treatment, the assumption did not follow correct clinical practice. Simpson (2004) has compared another PHAART based on lopinavir/ritonavir (LPV/r) to another PHAART based on nelfinavir (NFV) in combination with stavudine (d4T) and 3TC. The study concluded that the LPV/r based regimen gives an ICER of £4,250/QALYG compared to NFV based regimen which was cost-effective in comparison to the implied threshold of £25,000.

SUMMARY

It is clear from the above discussion that HAART has brought significant changes in health care costs since its introduction, by reducing hospitalization while increasing outpatient and medication cost. This increased need against a background of resource scarcity necessitates the question of choosing initial HAART regimen combination to be analyzed through an economic perspective. Information on the effect of HAART on preference based HRQoL is unfortunately still lacking as the existing literature focuses on the relationship between HIV severity and HRQoL.

Results from existing economic evaluations have confirmed that HAART is more cost-effective than the previous gold standard, monotherapy in lifetime period, thus establishing HAART as the treatment of choice in this era.

Ten years on and HAART is established as a necessary treatment for HIV patients with a multitude of drugs to choose to form the combination regimen. Patients now survive longer with different risks of ADE and death and with varying health needs. However, a question still remains on the effect of HAART, specifically different combinations of HAART on costs and quality of life of patients. The initial regimen of HAART served as focal starting point for many clinical investigations due to its long

lasting effect on the selection of subsequent regimens but unfortunately knowledge of the economic and quality of life outcomes were still lacking for different initial combinations. Several studies have explored by modeling on the effects of selected combinations on cost and quality of life outcomes but the rapid pace of clinical research has rendered the analyzed combination obsolete compared to current guideline recommendations. Research is therefore urgently needed to update knowledge and investigate the effects of different combinations of initial HAART regimens on the cost and quality of life of patients.

AIMS OF THE PRESENT STUDY

The aim of this study is to evaluate the effect of initial highly active antiretroviral treatment (HAART) regimens, specifically between protease inhibitor based regimens (PHAART) and non nucleoside reverse transcriptase inhibitor (NHAART) on the cost of treatment and quality of life of HIV patients. This will be operationalized in four specific objectives within four studies:

Objectives

Study 1 To evaluate the effect of different initial HAART regimens on patients' outpatient cost.

Study 2 To explore the effect of different initial HAART regimens on patients' HRQoL.

Study 3 To develop a HIV progression model to depict patients' clinical and treatment progression.

Study 4 To explore the cost of treatment and HRQoL of patients on a longer time horizon and evaluate the efficiency of PHAART and NHAART based on current recommendations.

Chapter 2

Study Rationale and Methodological Framework

INTRODUCTION

The natural history of HIV has changed tremendously with the introduction of highly active antiretroviral therapy (HAART). What was a highly acute and fatal disease now has become a chronic state of disease with increased survival rates and reduced acute AIDS defining events (ADE) (Moore and Chaisson, 1999). On the other hand, toxicity associated with HAART has adversely affected patient quality of life (Carr and Cooper, 2000). Consequently, survival and number of ADEs no longer suffice as measurements to monitoring HIV patient health. It is now realized that this should also include monitoring of patients' quality of life (Forum for Collaborative HIV Research, 1999b).

The initial HAART combination has been of special interest because of its effect on subsequent treatment selection. Currently, there are more than 25 antiretroviral drugs to choose for HAART combinations but recent guidelines have recommended either efavirenz based HAART combinations or ritonavir boosted lopinavir (LPV/r) based HAART combinations as initial regimens for treatment naïve HIV patients (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006, European AIDS Clinical Society, 2005, Gazzard et al., 2006). This is based on intermediate outcomes in the form of surrogate markers efficacy of both combinations i.e. viral load suppression in a few short clinical trials and observational studies.

In light of resource scarcity, whereby a choice has to be made for a combination of HAART, comparison by using these intermediate outcomes per se would ignore cost implications and effects on quality of life. A proper appraisal from an economic perspective would balance these health outcomes against their cost and shed light on the need for a choice that could maximize their benefit with the given resource. The previous chapter reviewed past studies which evaluated HAART effects on

of *Home management*, *Communication* and *Recreational activities* which is identical to that reported by Longstreth et al, 1992 who evaluated patients from a US neurology clinic and consistent with the analysis of most frequently endorsed items in this study. This is also similar to those reported for a group of patients with another chronic disease, rheumatoid arthritis (Deyo et al., 1982) and thus these similarities suggest that some of the dysfunction reported by PD patients may not be specific for PD but rather with chronic diseases in general. The main difference in this study was that the physical dimension impairment score was higher than the mean psychosocial dimension score. This may be explained by the mean age of the patients recruited from the UKPDS (70.5 years), which was noticeably higher than the mean age of patients recruited from the Longstreth study (66.3 years) and that these patients were recruited from a neurology clinic. Increasing age may result in worse physical scores whereas a younger population may be more aware of their psychosocial dimensions.

Less dysfunction was related to *Eating* and *Emotional behaviour*, which indicates that eating is not a problem associated with PD patients and that these patients are not emotionally disturbed in that they do not feel they are a burden to others or fearful of the future. Emotional behaviour is very dependent on a patients circumstances and health at a single point in time and should therefore be evaluated in more depth and detail than is in either of the HRQOL instruments. The UKSIP asks patients to describe how they are on the day of completing the questionnaire and therefore does not take into account the temporal nature of emotional behaviour and may therefore miss that a patient was worried about the future or nervous in the preceding week or month. The PDQ-39 asks patients how they were "during the last month" but addresses *Emotional well being* in 4 questions as apposed to the UKSIP *Emotional behaviour domain* which has attributed 9 items. The PDQ-39 could attribute further items to *Emotional well being* domain to capture whether the patients are irritable, blames themselves, gets sudden frights, or frustration. These items are addressed in the UKSIP but avoided in the PDQ-39. Adding items that identify different areas of the *Emotional well being* domain of the PDQ-39 will strengthen the comprehensiveness of the instrument, particularly as "current feelings of optimism" has been shown to have a significant impact on HRQOL (Findley and Committee, 2002). The coping strategies adopted by patients with chronic diseases are widely recognised as influencing their ability to maintain reasonable levels of emotional well-being (Felton and Revenson, 1984). It is feasible that patients with PD can adapt to their situation by lowering their expectations regarding their own physical capacity

these health outcome measures and cost implications in HIV patients. The present chapter will summarize the rational behind the current study and its general methodological framework.

STUDY RATIONALE

The critical review of the current state of knowledge in HIV management in the last chapter demonstrates a lack of studies evaluating the impact of different HAART combinations on the cost of treatment and quality of life of patients. Therefore, there is an urgent need to investigate the implications on clinical, economic and humanistic outcomes of different initial HAART combinations in HIV patients based on the following issues:

Exploratory Work

In view of the lack of long term studies and clinical trials assessing current initial HAART regimens effects on HIV patients, exploratory outcome assessment using appropriate statistical analysis, modeling and economic evaluation tools can all generate data to inform future trials and policy (Brennan and Akehurst, 2000).

Complexity and Rapid Change in HIV Management

In the relatively short period since HIV was first diagnosed, research into the field has generated more than a 2000% increase in published HIV related scientific articles. The current management of HIV infection not only includes a cocktail of at least three antiretroviral drugs, but also a complex monitoring regime for surrogate

markers, opportunistic illness, immune recovery illness, resistance, adverse drug reactions and HIV progression (see previous chapter).

Current guidelines recommend either lopinavir – ritonavir or efavirenz based regimens as an initial treatment in treatment naïve patients (Gazzard et al., 2006, Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006). However, no large long term randomized comparative study has been performed to deal with these two profoundly different therapeutic strategies (the first based on a boostered protease inhibitor, and the second on a non-nucleoside reverse transcriptase inhibitor), with regard to both efficacy and tolerability issues. Furthermore, newly described adverse events and pill burden will have an adverse effect on patient adherence and resistance, consequently leading to a potential therapy failure. These factors need to be accounted for in treatment decision-making.

Changes in HIV Natural History

New treatment strategies with HAART have dramatically diminished the morbidity and mortality associated with HIV-1 infection resulting in a change from a previously acutely fatal disease into a chronic state of disease. The estimated incidence of AIDS opportunistic illness declined 6% during 1996 compared with 1995, and estimated deaths decreased 23% during the same period (Cheever, 2002, Cauda et al., 1999, Castagna et al., 2002, King et al., 2003). This could lead to a change in the pattern of resource utilization and its effect on patient health outcome.

Multidimensional Impact of HIV Infection and Treatment

Different HAART treatments can not only differentially affect patient mortality and morbidity, but can also affect different economic outcomes such as administration

and antiretroviral drug procurement costs, adverse drug reaction monitoring and treatment, laboratory monitoring, health professional time, hospital bed occupancy and palliative care support (Beck et al., 1998c). Patients with HIV have also been shown to have worse quality of life than other chronic disease patients (Hays et al., 2000).

Resource Scarcity

Complex antiretroviral and monitoring regimes are taxing on an already stressed health authority fund. The potential 'opportunity cost' arising from choosing a HIV regimen can be seen in relation to the benefits forgone from HIV services e.g. HIV prevention and from other health care services e.g. diabetes palliative care. This leads to further issues such as selecting the components affected, rebalancing the resources involved, and also analyzing the worth of one service over another against losing the benefit of others.

METHODOLOGICAL FRAMEWORK

HRQoL Preference Based Instrument

The Quality adjusted life year (QALY) is an outcome measurement that combines mortality (life expectancy) and health-related quality of life (HRQoL). Whilst mortality measurement is straight forward, many instruments and methods exist to measure HRQoL.

The instruments measuring HRQoL generally belong to three broad categories. The first are usually measured through various psychometric methods which only give a

descriptive profile on various dimensions of HRQOL (Richardson et al., 1998). One of the most popular instruments in this category is the SF-36. Another instrument commonly used in HIV is the MOS-HIV that includes domains specific to HIV e.g. energy/fatigue, cognitive functioning, health distress and quality of life. The second category is an economic method which is based on the von Neumann-Morgenstern utility theory (Drummond et al., 1997). Instruments in this category include the direct preference elicitation i.e. Time Trade-Off (TTO), Standard Gamble (SG) method and indirect preference elicitation i.e. multi-attribute instruments such as the Health Utility Index and EuroQOL (Drummond et al., 1997). This category is more useful in an economic evaluation as it gives a single index to quality of life and also because it is based on economic principles. The third category contains instruments that have sought to indirectly estimate a patient's HRQoL. One of them is the 'quality-adjusted time without symptoms of disease or toxicity of treatment' (Q-TWiST) instrument which estimates HRQoL from the patient's drug toxicity experience (Messori et al., 1997). In this method, HRQoL of patients are obtained by calculating patients' survival time without experiencing symptoms of disease or toxicity of treatment using a range of intermediate weightings. This method has been criticized as it is not based on patient preference (Messori and Trippoli, 1998) and on its assumption of toxicity experience as the only dimension related to HRQoL.

As the present study has been undertaken in an economic framework, only instruments in the second category were considered. In choosing an appropriate HRQoL instrument for this study, five important factors needed to be taken into consideration (Richardson et al., 1998).

- A valid and reliable measure of the strength of preference for a health state

- Sensitivity to changes in the health state
- The existence of an interval property
- Ability to verify and reproduce results and minimize possible gaming by interested parties
- Comparability between scores derived in different studies

This section will briefly review four of the most common economic HRQOL instruments: Health Utility Index 3 (HUI3); EuroQoL; Standard Gamble; and Time Trade-Off.

Standard Gamble

Standard gamble is a classic and direct method of measuring cardinal preference (Drummond et al., 1997). The standard gamble technique (SG) is based on the assumption that individuals maximise expected utility under uncertainty.

Under this assumption, when individuals are indifferent between two options one may infer that the utility of each of them is the same. Using this premise, subjects are asked to make pairwise comparisons between states of illness and full health. For each state of illness, the subjects are offered two alternatives:

Alternative 1 is a treatment with two possible outcomes: either the patient is returned to normal health and lives for an additional t years (probability p), or the patient dies immediately (probability 1-p);

Alternative 2 has the certain outcome of health state i for t years. The task is to establish the value V(i) of state i. Probability is varied until the subject is indifferent between the two alternatives. At this point, expected utility is assumed to be the

same in both options: p x 1 + (1-p) x 0 = 1 x V(i). This yields a value for state i at time *t* (Drummond et al., 1997).

Time Trade-Off (TTO)

The time trade-off technique (TTO) works similarly, but uses time instead of certainty for the trade-off. Two alternatives are offered.

One is living in state of illness i for time T followed by death, the other is living as healthy for a shorter time t, followed by death. Time t is varied until the respondent is indifferent between the two alternatives, at which point the value of the two scenarios is assumed to be the same: V(i) x T = 1 x t. This yields a value of t/T for state i (Drummond et al., 1997).

Health Utility Index 3 (HUI3) and EuroQoL (EQ-5D)

The Health Utility Index 3 (HUI3) and EuroQoL are both multiattribute utility instruments. Attributes with different severity levels are used to define health. The scores and attributes were derived from the preferences of members of the general public.

The HUI3 consists of eight attributes: vision; hearing; speech; mobility; dexterity; emotion; cognition; and pain, with each having five to six levels (Feeny et al., 2002). This gives 972,000 theoretical numbers of different health states. It was derived from standard gamble preferences of 500 Canadians.

EQ-5D (EuroQOL) consists of five attributes with three levels: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. The theoretical number of different health states able to be defined through this instrument is 243. Population

preferences were elicited by time trade-off method of 3,000 individuals in the United Kingdom.

HRQoL Instrument of Choice for This Study

With the criteria outlined by Richardson (1998) in mind, the method chosen for HRQOL elicitation in this study would be the HUI3. As with the EQ-5D and other instruments, the HUI3 has been validated in the United Kingdom and also in the HIV population (Feeny et al., 2005). Compared to direct methods i.e. SG, and TTO, the HUI3 was found to be sensitive to changes in HIV stage and is well correlated with the MOS-HIV (Bayoumi and Redelmeier, 1999). In performance comparisons between the HUI3 and the EuroQol, both demonstrate excellent selectivity and sensitivity on the receiver operating characteristics curve (Houle and Berthelot, 2000). The two however differed in the cumulative distributions curve and independence between dimensions. The curve of EuroQoL is stepwise but the HUI3 curve is smooth and the closest to a continuous curve. EuroQOL gives a substantial linear correlation ($r>0.25$) for 9 out of 10 cross comparisons, suggesting the instrument taps into fewer than the five dimensions. HUI3 has only 2 of the 26 possible cross comparisons with linear correlations – showing all its eight attributes to be virtually independent. Finally, the theoretical number of different health states is 243 for EuroQoL and 972,000 for the HUI3, suggesting HUI3 to be more sensitive to patient health state.

Cost Analysis Methods

There are several potentially important challenges in the statistical analysis of cost data. Firstly, cost data is typically right skewed, with very few patients incurring the

highest costs (Drummond and McGuire, 2001). The distribution also tends to exhibit large variability that can be problematic for the estimation of precise cost differences with the appropriate statistical power. This variability often results in a high increase in mean cost that would eventually make it impossible to use the normalizing and variance stabilizing transformation technique. Hence, methods that assume a normal distribution and equal variance, such as linear regression, analysis of variance and Student's *t*-test may not be appropriate. This assumption is problematic as the distribution for time to an event might be quite dissimilar from the normal, whereby they could be non symmetric, or bimodal and linear regression is not robust to these violations (Cleves et al., 2004).

Another important consideration to be made in estimating cost is that the study is prone to censoring. If ignored, the effect will lead to estimates of study endpoints that are biased towards individuals with shorter (complete) survival times. Censoring can occur when patients do not experience the event of interest in the study period. There are four mechanisms under which censoring can happen (Young, 2005). Random censoring occurs when patients are lost at any time during the study period because of reasons unrelated to the event of interest. Censoring can also occur because of study period restriction. Any patient withdrawal from the study related to event of interest is called informative censoring. Another censoring mechanism is usually found in economic evaluation where either the economic or effectiveness outcome is not complete.

Finally, as the same individual's variables are measured repeatedly over time, these multiple observations are typically correlated leading to potentially exaggerated statistical significance of the observed differences (Liang and Zeger, 1986). The correlated observations could also lead to incorrect inferences about regression

coefficients and inefficient estimates of β (Diggle et al., 1996). Standard regression analysis assumes that all observations in the sample are independent which occurs in most repeated measurement studies.

There are two longitudinal methods usually employed in cost analysis – the first is based on the survival analysis technique while the other is based on the multilevel model (MLM) (Drummond and McGuire, 2001). However, methods involving estimators of discrete and continuous time survival analysis that concern event occurrence are unsuitable for studying systemic change of cost over time (Singer and Willett, 2003). Furthermore, heavy censoring due to non event occurrence was expected in this study because of its short duration, which would lead to bias in estimation (Young, 2005).

Method of Choice for This Study

Based on the above reasons, a longitudinal approach using multilevel modeling (MLM) will be used in the analysis of HIV patients' outpatient care costs. This approach will allow an answer to the research questions regarding: within patient cost summary (how does the patient cost change over time); and between patient comparison (how do these trajectories differ by patient characteristics).

MLM comes under many different names. Random effect model, hierarchical linear model, mixed model and random coefficient model are some of the terms that refer to the same method (Ekuma and Lix, 2004).

MLM has typically been used in education research but has more recently been used in the medical field. It is particularly suited to analyzing data from repeated measurements or data in a hierarchical structure. For example, in multicentre clinical trial research, patients are considered as a component of level 1 that are grouped

within a higher level 2 i.e. hospital. This could later be grouped within another higher level 3, in this case representing country (Figure 2.1). MLM takes into account that patients from the same hospital or country have more in common than patients who are randomly sampled from a larger population.

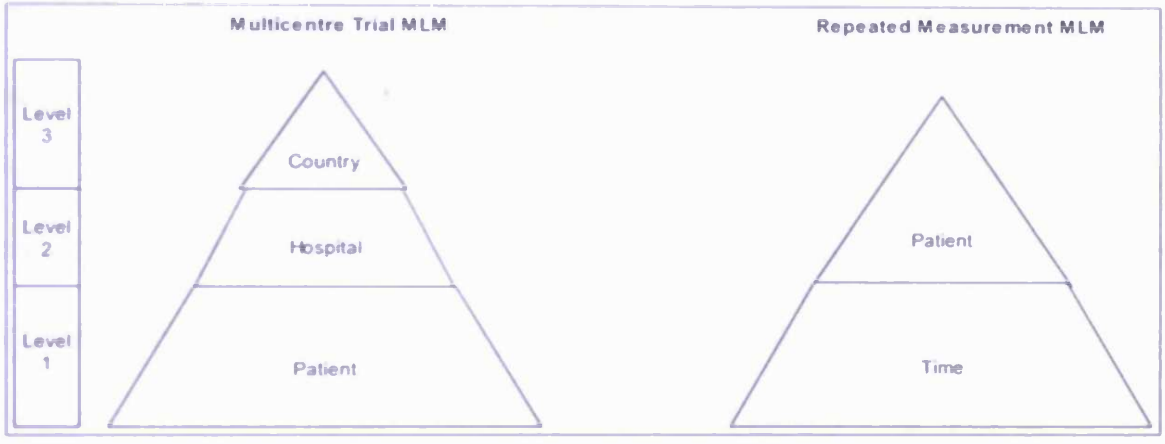


Figure 2.1 Illustration of multiple levels modelling data hierarchy

In a longitudinal study whereby repeated measurement for the same individuals occurs, the method could be applied to allow analysis of changes between individuals and within individuals. Time or measurement occasions would then be in level 1 whilst patients would be represented in level 2 (Figure 2.1).

The level 1 component in the multilevel model of longitudinal data, also known as the individual growth model, is the change that each member of the population is expected to experience during the time period under study (Singer and Willett, 2003). For example, we could write a level 1 sub model for monthly cost as below:

$$Y_{ij} = [\pi_{0i} + \pi_i(TIME_{ij} - 1)] + [\varepsilon_{ij}]$$

In the above model, we postulate that in the population from which this sample was drawn, Y_{ij}, the value of monthly cost for patient *i* at time *j*, is a linear function of his age on that occasion ($TIME_{ij}$). This model also assumes that a straight line could adequately represent each patient's true change over time and that any deviations from linearity observed in sample data result from random measurement error (ε_{ij}).

The bracket ([ ]) distinguishes the sub model into the structural part and the stochastic part. The structural part represents the hypotheses about each person's true trajectory of change over time. In the above model, it stipulates that this trajectory is linear with time and has individual growth parameter π_{0i} and π_{i} that characterize its shape for the *i*th patient in the population. The intercept, π_{0i}, would therefore represent patient *i* true monthly cost at time 0. The slope, π_{i}, meanwhile would represent the rate at which patient *i* changes over time.

The level-2 sub model which includes the patient as a unit of analysis describes the relationship between interindividual differences in the change trajectories and time-invariant characteristics of the individual. Following the previous example, we could add another explanatory variable, i.e. TREATED to postulate a level 2 model which could be written as below:

$$\pi_{0i} = \gamma_{00} + \gamma_{01} TREATED_{i} + \zeta_{0i}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{11} TREATED_{i} + \zeta_{1i}$$

Taken as a whole, the two sub model 2 components regard the intercept π_{0i} and the slope, π_{1i} of patient's individual growth trajectory as level 2 outcomes that may

be associated with the predictor, *TREATED*. Each component permits level 1 parameters (π) of an individual to differ stochastically from others with its own residual (ζ_{0i} and ζ_{1i}).

Systematic interindividual differences in change trajectory according to values of the level 2 predictor was captured by fixed effect (that assumed constant error term over time), which in the level 2 model is defined as $\gamma_{00}, \gamma_{01}, \gamma_{10}$ and γ_{11}. In the above example, the slopes would represent the effect of predictors *TREATED* on the individual growth parameters.

Analysis of Quality of Life

As described in the previous section, conventional statistical techniques were unsuitable for analysis of longitudinal data. In the analysis of patient quality of life, multilevel models were extended for this purpose.

In fact, multilevel models were evaluated previously for analysis of quality of life data, specifically the Health Utility Index and were deemed highly suitable for analysis of quality of life (Vermeulen et al., 2005).

Lifetime Cost and Life Expectancy Projection Methods

Ideally estimates of survival and lifetime cost needed for cost-effectiveness analysis would use evidence from trials or longitudinal studies. But such studies can be excessively long (and thus expensive) to ensure all extra survivors die by the end of the trial and hence are only suitable for conditions with very short survival rates. Furthermore, it is unclear whether the relative magnitude of incremental costs and

outcomes observed during the study would be reflective of what would be observed had the study been continued until all study subjects died or discontinued therapy. Ordinary regression models require preliminary parametric assumptions such as a preset time point for the change in the slope of CD4 cell count for linear models. One of the methods proposed was to fit data using flexible survival or proportional hazard (PH) models. However, it has been noted that using a surrogate marker such as CD4 count as a marker covariate in PH model is not fully justified, as they are considered as 'internal covariate' for the corresponding lifetime variable (de Waal, 2001. p 5). Furthermore, as the study period is short, most patients will not experience event at the end of study.

A decision analysis model approach has increasingly been utilized in solving health care problems. This method involves a systematic, explicit and quantitative approach for decision-making under uncertainties (Siebert and Sroczynski, 2005). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices defined modeling as 'an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources, and whose purpose is to estimate the effects of an intervention on valued health consequences and costs' (Weinstein et al., 2003).

Two basic forms of this are decision trees and Markov models. As decision trees are limited to solving simple problems with no time dependent parameters and fixed time horizons, Markov has been more widely used to estimate lifetime cost and survival, especially in chronic diseases such as HIV where events can occur repeatedly over time.

Recent models used to study HIV disease progression are mainly Markov models (Shechter, 2006, Fernandez Lison et al., 2005, Yazdanpanah, 2004, Simpson et al., 2004, Corzillius et al., 2004, Jeffrey et al., 2003, Richter et al., 2002). This interest lies in the fact that HIV inherently has ongoing risks over time e.g. risk of developing Kaposi's sarcoma or oral candidiasis. Consequently, there is uncertainty in the time of event occurrence which would have important implications since utility of an outcome often depends on when it occurs. For example, an AIDS defining illness occurring when one is 20 years old would have a different impact if it occured 20 years later.

Another consequence of an ongoing risk is that a given event may occur more than once. Markov models conveniently accommodate ongoing risk by assuming that patients are always exclusively in one of the finite health states during an equally divided period of time (cycle). During each cycle patients may transit to another health state or remain in their present state given transitional probability (Sonnenberg and Beck, 1993).

Markov models comprise a set of mutually exclusive and collectively exhaustible health states. Each person in the model must reside in only one health state at any point in time. The person transits among the health states at a fixed incremental time (Markov cycle length) according to a set of transitional probabilities. By assigning numeric values to a series of health states over time, Markov models allow for the synthesis of data on costs, effects and HRQoL of alternative clinical strategies through the calculation of life expectancy, QALY and lifetime costs – making it an ideal economic evaluation tool. Furthermore, it allows synthesis of information; revealing logical connections between input and output while allowing for the flexibility of different assumptions about treatment efficacy over time.

There are two methods commonly used for Markov model evaluation (Drummond and McGuire, 2001). Firstly, through cohort simulation that tracks a hypothetical cohort of patients simultaneously through the model. The initial cohort would be first 'seeded' among the starting health states. In subsequent cycles, the transition probabilities specified by a matrix would partition the cohort in the new initial state as a fraction of the previous cycle cohort. The outcomes accrued in a cycle would be totalled to give a cumulative utility (Sonnenberg and Beck, 1993).

The second method of evaluation is through Monte Carlo simulation that randomly selects a patient from a hypothetical cohort and simulates each patient, one at a time through the model. It records the outcome for each patient depending on the particular pathway he took through the health states prior to dying.

In comparison to Monte Carlo, cohort simulation is faster and more transparent. However, it has the disadvantage of requiring each health state to describe all relevant current and past clinical information resulting in a very complex and 'bushy' model structure. In contrast, Monte Carlo simulation allows the information to be included as a tracker for each patient transitioning in the model.

Therefore, in order to explore long term outcomes of HIV patients, the Markov Monte Carlo simulation model will be adopted.

Economic Evaluation Methods

The target program is the selection of the initial HIV treatment combination choice of either PHAART or NHAART. HAART treatment not only affects antiretroviral drug procurement cost, but also other resources e.g. adverse drug reaction monitoring and treatment, laboratory monitoring, health professional time, hospital bed occupancy and palliative care support (Beck et al., 1998c). Some resources might

see an increase in utilization whilst others may see savings from the treatment. Given scarce resources, a rational decision has to be made and one of the criteria for the evaluation of this choice could be efficiency. The aim is then to maximize the benefit to any resource expenditure or minimize the cost of any achieved benefit.

In short, the search is for technical efficiency – how best to make use of given resources? There are three economic evaluation tools that are used to address this question, namely cost minimization analysis (CMA), cost-effectiveness analysis (CEA) and cost utility analysis (CUA) (Briggs and O'Brien, 2001).

Cost minimization analysis is only used when the health effects are known to be equal between comparators and only costs are compared. Hence in CMA, only the least costly treatment would be chosen. On the other hand, both CEA and CUA examine the cost and consequences of health programs or treatments of interest (Drummond et al., 1997).

The main difference between CUA and CEA is that CUA incorporates the notion of value in its outcomes, in contrast with CEA's outcomes which are single, program specific and unvalued. Whereas CEA outcomes deal with natural units such as life expectancy, or number of events averted, CUA's outcome, is normally expressed in Quality Adjusted Life Years (QALY).

QALY is an outcome that was created to incorporate both morbidity (quality of life) and mortality (life expectancy). It therefore takes one year of perfect health-life expectancy to be worth 1, but regards one year of less than perfect life expectancy as less than 1.

This QALY outcome will be especially beneficial in an HIV infection context, because each treatment combination has a different adverse reaction and effectiveness profile that will have a significant impact on subsequent second line

combinations where the failure of one might render the virus resistant to a particular drug (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006).

Adopting the social welfare basis, where cost should include all resources accrued and benefits should encompass all benefits, a careful evaluation of the economic, clinical and humanistic outcomes is needed to assess and compare the combination efficiency.

As the effects of both choices of initial regimen are known to be substantially different, CMA will not be considered. The present study will utilize both CEA and CUA to evaluate the choice between initial PHAART and NHAART.

STUDY PLAN, DATA PROCESSING AND ANALYSIS

Hypotheses

The research will address the following hypotheses:

- Different initial regimens will have different effects on patients' outpatient monthly cost.
- Different initial regimens will have different effects on patients' quality of life (patients' health state preference).

Ethical Consideration

Prior to commencement, this study was approved by the South East Wales Research Ethics Committee and local hospital administrator on the 24th September

2004 (Ref: SMKW/EL/jl/04/WSE03/71). A copy of the ethical approval is attached in Appendix I.

Study Design

This research was designed as both a prospective longitudinal study of health related quality of life (HRQoL) and a retrospective study of health care resource utilization by patients receiving HIV care in Cardiff Royal Infirmary (CRI) and University Hospital of Wales' (UHW) outpatient clinics.

These two clinics oversee the care of more than 50% of Wales' 672 HIV patients with 254 patients routinely receiving care in the trust's primary HIV outpatient clinic in Cardiff Royal Infirmary (Health Protection Agency, 2004).

Patients were approached in the regular HIV outpatient clinic in the hospital following identification and an introduction by clinic staff in the interests of privacy and confidentiality. The patient was briefed about the study in the clinic and given a printed study information sheet (Appendix II).

Patients were only included in the study if they gave written informed consent (Appendix III).

Inclusion and Exclusion Criteria

All patients receiving outpatient HIV care in CRI and UHW during the study period (1st November 2004 to 31st August 2005) were eligible for the study.

Patients aged less than 18 years old were excluded from the study. In addition, patients that were mentally challenged with impaired judgement or physically unconscious were also excluded. Seriously or terminally ill patients were only included if they were able to give informed consent.

Sample Size

As with cross-sectional studies where prior knowledge of the number of subjects are required to achieve a specified statistical power, longitudinal studies also require sample size calculation. This is essential as a study with too small a sample would give inconclusive results whereas an excessively large sample size could just simply waste research resources (Fayers, 1993).

The calculation of sample size for longitudinal studies however is a bit different from cross-sectional studies in that it also needs to consider the variations and correlations introduced by repeated measurement (Diggle et al., 1996). The formula for sample size calculation is as follows:

$$m = \frac{2(z_{\alpha} + z_{Q})^2[1 + (n-1)\rho]}{n(\Lambda^2)}$$

Where $\Delta = d/\sigma$, is the smallest meaningful difference in SD unit. This is obtained by dividing the smallest meaningful difference of interest to be detected, d with measurement variation, σ. ρ, is the correlation among the repeated observations, and α, is the type I error rate. Q is obtained by subtracting P, statistical power to reject the null hypothesis when it is incorrect from 1 (i.e. $1 - P$).

Missing Information

Missing data is information that is not available for a subject or a case. Its occurrence could result in the loss of statistical power and potentially leads to bias, hence the need to identify and properly handle it. It used to be an accepted practice

to analyze data with missing values using 'complete case analysis', whereby an individual's data which had any of the required variables missing was omitted from the final analysis.

This approach however can lead to bias in the conclusions of the study, by excluding individuals whose patterns of association may be different to those retained, at best leads to loss of precision due to the reduction in sample size available for analysis (Allison, 2001).

There are three patterns of missing data, namely, Missing Completely At Random (MCAR), Missing At Random (MAR), and Not Missing At Random (NMAR). They are defined by the mechanism of the missing data or in other words why the data are missing. For example, when modelling Y as a function of X, the data is said to be MCAR if there is no relationship of Y missing to either X or Y. If the probability of Y missing is only due to X, then such data are called MAR. However, if the probability of Y depends on the unobserved value of Y itself, then the data is an NMAR. Missing data patterns will determined the way they are approached whereby MCAR and MAR usually means that the information available are good predictors of missing data and imputation is possible.

In this study, collected data were examined for patterns of missing data in STATA's *mvpatterns* module. Missing values were then manually inspected for possible logical deduction or completion of dataset from source. Following this step, the data set were further diagnosed for randomness of missing values by dividing the dataset into a group with missing values for a specific variable and another group with valid values of the variable. If patterns of significant differences are found between the two groups, on other variables of interest, it would indicate a NMAR data.

Methods to handle missing data should consider the variation and uncertainty associated with the missing parameter estimates (Allison, 2001). There are two methods recommended to estimate missing data with MAR and MCAR patterns: firstly, through maximum likelihood; and secondly by multiple imputations. In maximum likelihood, all plausible values are integrated, giving more weight to values that are more plausible. Multiple imputations can be considered as approximations of maximum likelihood whereby a few plausible values are tried wherever they are missing. A disadvantage of maximum likelihood is that it requires restrictive missing data distribution assumptions. For flexibility reasons, missing data in this study are handled through multiple imputations.

The multiple imputations are employed using the chained equation (ICE) method on all variables with at least two occurrences in this study. In this approach, several single imputations are carried out on the same incomplete data set - each time imputing different values, and obtaining different parameter estimates from fitting the model. The variation between the parameter estimates from different imputations is an estimate of imputation variance. Total variance of the parameter estimates would later be calculated based on the estimates of sampling variance and imputation variance to give the plausible imputation values for the missing data.

There are two major approaches usually used for multiple imputation (Kofman and Sharpe, 2003). The first approach is based on the joint distribution of all variables considered in the analysis. The second approach, which is taken by ICE is based on each conditional density of a variable given all other variables. In order for ICE procedure to create an imputed data set for multiple variables x_1, x_2, ..., x_k, with missing observations, it will (Royston, 2005):

- Ignore observations for which every member of x_1, x_2, ..., x_k has a missing value. This step will eliminate the observations that are impossible to impute;
- For each variable with any missing data in x_1, x_2, ..., x_k, ICE will randomly order that variable and replicate its observed values across the missing cases. This step initializes the iterative procedure by filling in missing data at random;
- For each of x1, x2, ..., x_k, in turn, ICE will impute missing values by with the remaining variables as covariates by an appropriate regression model. The model can be ordinary least square (OLS) if the imputed variable is a continuous variable or a logistic model if it is a binary variable.
- The steps above are repeated # times specified by the **cycles (#)** option. This is set at 5 imputations in this study.

Further statistical analysis on multiple imputed data was based on the combined dataset estimates using STATA's ***mim*** module.

Following the preceding methodological review, the work will include four studies:

Study I Resource utilization and cost analysis

Study II Quality of life of patients with HIV

Study III Modelling framework of HIV progression

Study IV Lifetime Cost-effectiveness and Utility Analysis

Study I: Resource Utilization and Cost Analysis

Objective

To evaluate the effect of different initial HAART regimens on patients outpatient cost.

Hypothesis

Different initial HAART regimens give different outpatient costs.

Time Frame

Patients will be identified by the physicians at the clinic's and will be included in the study upon their consent. Patients' resource utilization records will be charted from 1st January 1996 or the date they first receive care in the clinic whichever comes later. The date was chosen as the HAART combination is only available from this date. Data will be collected until the date of the patient's death; the date the patient is determined to have left the cohort due to loss to follow-up; or the end of the data collection period (31st December 2005), whichever is the earliest date.

Perspective

Whilst it is often recommended that the economic evaluation takes a broad societal perspective (Drummond et al., 1997), the presence of limited funds in a health authority results in decision makers often being primarily concerned with costs that will directly accrue on the health service, as any savings beyond this can not be accrued to balance the acquisition cost. This economic evaluation therefore will be conducted from the institutional perspective of Cardiff Royal Infirmary and the

University Hospital of Wales. Consequently, community care and patient-specific utilization will not be accounted for the analysis.

Data Collection Methodology

Clinical, economic and demographic data will be abstracted from patients' medical records and recorded into a specially developed electronic research database (Appendix IV). This database will be developed using Microsoft Access Version 2002 and protected by a secure password system available only to the principal investigator and principal physician. The following data will be recorded in the database:

- Clinician treatment plan (antiretroviral drug, ordered laboratory test)
- Patient's medical history (first diagnosis date, HIV related medication, opportunity disease)
- Laboratory indices (CD4+, viral load, liver test value, renal test value, genotype resistance test results)
- Demographic characteristics (age, ethnicity, occupation, nationality and risk factors)

Clinical outcome data will be continuously collected until the patient dies or six months follow up period is completed. Any hospital based activity including outpatient visit, in patient admission and laboratory test will also recorded and the same in-clinic procedure will be followed.

Resource Valuation

In costing studies, monetary values are attached to the health care resources utilized. Economists argue that the economic definition of costs as the benefits forgone (opportunity costs) should be used in costing studies. Price in a perfect market is a good estimate of opportunity cost because the market is in equilibrium (producers are able to sell all that they want and consumers are able to purchase all they wish) and the purchaser is the price taker (Mogyorosy and Smith, 2005). However, the perfect market does not exist in health care partly due to the uncertainty involved in one's health, imperfect knowledge on the part of the consumer regarding his health status and care options, and lack of competition in the health care market (Donaldson and Gerard, 1994).

There are several ways resources are valued in practice e.g. charges or market price, use of fee, using standard costs, and estimation from literature (Mogyorosy and Smith, 2005). The selection of resource valuation methods is determined by the research question, the estimated impact of the unit costs on the total costs, representativeness, and the availability of data. This study will value resources based on list price and standard tariff as recommended in UK practice (Mogyorosy and Smith, 2005) due to the availability of data and to increase the external validity of the results. All costs will be expressed in 2007 British pounds.

Medication Costs

Only antiretroviral utilization will be charted from patient medical records. Drug cost is valued based on the standard adult daily dosage in the current British National Formulary (Joint Formulary Committee, 2007). It is important to note however that the British National Formulary's price is the manufacturer's list price and does not

reflect the actual cost bourn by the trust. The actual medication cost not only includes the drug acquisition cost paid by the trust to the supplier but also takes account of the discount rate, tax, retailer mark up, the cost of dispensing and also the fact that some antiretroviral drugs are provided as free samples.

Outpatient Costs

Outpatient costs will be determined by calculating bottom up outpatient cost for both clinics based on mean clinic attendance for a year, and personnel costs which are valued using a well established UK personnel tariff (Netten and Curtis, 2006).

Investigation Costs

Costs for laboratory and radiology investigational procedures were obtained by multiplying the number of tests or procedures by the unit costs for the trust and national tariff (Department of Health, 2005a, Department of Health, 2005b, McDowell, 2004, Newcastle Upon Tyne Hospitals NHS Trust, 2006, The University College London Hospital NHS Foundation Trust, 2005). The relevant selected tariffs in the national reference cost are presented in Table 2.1.

Cost Analysis

Although routine clinic outpatient visits usually occur every three to six months, some monitoring procedures require a more intensified regime for patients with certain treatment phases. Therefore, the unit of time for cost analysis will be monthly cost to reduce statistical variance. Descriptive statistics will be used initially to explore the pattern of cost among patients and also to determine random empirical cost trajectories for patients. The exploratory longitudinal analysis of cost data is

also useful 'to highlight aggregate patterns of potential scientific interest' (Diggle et al., 1996).

Table 2.1 Investigational medical procedures national tariff

INVESTIGATIONAL RESOURCES	TARIFF (£)	INVESTIGATIONAL RESOURCES	TARIFF (£)
Radiology		Laboratory	
Band A	17.00	General Pathology	2.01
Band B3 - Other Ultrasound	36.00	Chemical Pathology	2.76
Band B4 - Other Band B Tests	33.00	Haematology	3.74
Band C2 - Ultrasound	69.00	Histology / Histopathology	20.27
Band C3 - CT Pulmonary Angiography	99.00	Immunology	8.64
Band C5 - CT Other	69.00	Microbiology / Bacteriology	7.92
Band C6 - Other Band C Tests	74.00	Neuropathology	13.55
Band D1 - CT	120.00	Phlebotomy	10.85
Band D4 - Other Band D Tests	128.00	Virology	7.97
Band E	229.00	Biochemistry	2.32
Band F1 – MRI	352.00	Other	6.07

Data will be analyzed for changes over time and fitted with other time variants (variables that change with time e.g. CD4+ count, viral load, antiretroviral regimen, age) and time invariant (variables that unchanged with time e.g. sex, ethnicity, nationality) explanatory variables to explain the changes of cost using multilevel model. The statistical model will be fitted using *xtmixed* module in STATA Intercooler 9.1. Model will be evaluated using *t*-statistic for each variable's parameter statistical significance in the model. Wald statistic will be used to evaluate overall model fitness.

Study II: Quality of Life of Patient with HIV

Objective

To explore the effects of different initial HAART regimens on patients' health related quality of life (HRQoL).

Hypothesis

Patients receiving different initial HAART regimens have different HRQoL.

Data Collection Methodology

Participating patients will be required to complete the demographic (ethnicity, nationality, and risk factor) information form (Appendix V) and Health Utility Index Mark 3 (HUI3) questionnaires (Appendix VI) upon consent. Patients will also be required to complete HUI3 questionnaire at three and six month follow-ups.

The initial questionnaire will be completed by the patient in the presence of an investigator for initial guidance and supervision purpose. The follow-up questionnaire, with a prepaid envelope, will be given to the patient at this time but this will only be completed and mailed at the follow-up.

The HUI3 is a self administered questionnaire but where necessary the investigator will assist in completion. Scores for each HUI3 attribute as completed by patients will be recorded into the previously developed research electronic database and will generate the global multiattribute HRQoL score based on a given formula.

Time Frame

Patients will be identified by the clinic's physicians and included in the study upon consent (Appendix III). Patients HRQoL will be assessed on the consenting date as baseline and at three and six month follow-ups.

Quality of Life Analysis

Multiattribute utility will initially be calculated based on a published algorithm (Feeny et al., 1995, Feeny et al., 2002). Descriptive statistics will be used to explore the pattern of quality of life among patients and also to determine random empirical quality of life trajectory for patients.

HRQoL data will initially be fitted using cross sectional multivariate regression analysis. Data will later be analyzed for changes over time and fitted with other time variant and time invariant explanatory variables to explain the changes in HRQoL over time. A statistical mode based on multilevel model of change will be fitted using *xtmixed* procedure in STATA Intercooler 9.1. The best model fit will be evaluated using single parameter *z*-statistic test and Wald test.

Study III: Modelling Framework of HIV Progression

Objective

To develop a HIV progression model to depict patient's clinical and treatment progression.

Model Development Methods

Study I is a cost analysis of 9 years of patients health care resource utilization and study II involved analysis of quality of life of patients with six months follow up period. In order to enable exploratory and extrapolation analysis of cost and quality of life estimates from previous chapters at a longer time horizon, a Markov Chain Monte Carlo (MCMC) model of HIV progression will be developed using specialized decision analysis software (Treeage Software, 2007).

The model is based on previous models (Richter et al., 2002, Simpson et al., 2004) with updates on the disease processes based on current guidelines (Gazzard et al., 2006, Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006) and other published literature. Its development will adhere to the principle of decision analysis best practice which gives transparency to the model structure, data source and validation (Weinstein et al., 2003, Garrison, 2003).

The end model will be validated for convergent validity (the degree to which an operation is similar to other results that it theoretically should also be similar to) using non treatment options against the results of previous studies. The non treatment survival will also be compared to treated patients for face validity. The model is said to have face validity if it "looks like" it is going to measure what it is supposed to measure.

In order to assess internal consistency (the extent to which tests or procedures assess the same characteristic, skill or quality) of the model, the mortality probability in the model will be replaced with zero and the model is expected to give survival outcomes of zero as well.

Study IV: Lifetime Cost-effectiveness and Utility Analysis

Objective

To explore the cost of treatment and HRQoL of patients in a longer time horizon and evaluate the efficiency between PHAART and NHAART based on current recommendations.

Background

A long term outcome such as life expectancy and quality adjusted life years (QALY) is recommended to conduct an economic evaluation rather than intermediate outcomes e.g. surrogate markers. However, HAART is a relatively new treatment strategy and rapid turn out of new HIV drugs means that clinical and research experience with HAART combinations is considerably lacking. Furthermore, the efficacy of HAART has dramatically reduced the mortality rate of HIV patients and this means that a study which has to capture a long term effect of the drug would be excessively long and expensive. Therefore, there is a need to project the intermediate outcome into end outcome and this is achievable through modelling.

There are many approaches to model lifetime estimates of cost and life expectancy. Statistical model, decision tree, and Markov model are among the methods variably used for this purpose. The Markov model is deemed to be an appropriate model for this study as it is able to accommodate recurring events typical of chronic diseases as seen in HIV infection.

In this study, a Markov Chain Monte Carlo (MCMC) model developed in study III will be employed to explore the outcomes in longer time horizon. A randomly selected hypothetical patient with stochastically drawn CD4+ count and viral load will be simulated with varying risk of progressing to an AIDS defining event (ADE), and death. Each individual in the health state will either remain in the health state or move to another state according to assigned transitional probability at the end of the monthly cycle.

States Rewards

Each health state has a utility (HRQoL) score and a particular cost associated with it. The value of chronic cost and quality of life will be based on estimates in study II and III. Acute state costs and quality of life which were not available from the present study were sourced from external studies.

Discounting

The reason for the need to discount in an economic evaluation is 'time preference' which refers to the desire to enjoy benefits in the present while deferring any negative effects of doing so.

Discounting is not an adjustment for inflation. It is a technique in economics that is used to reflect the present value of a cost or health benefit that will occur at some future date (Drummond and McGuire, 2001). Future costs are discounted to account for the time value of money, and future health benefits are discounted to account for the delay in satisfaction from these outcomes. The effect of discounting is to give future costs and health benefits less weight in an economic analysis.

Discounting needs to be taken into consideration especially in a long time horizon study such as the present study that takes a lifetime time horizon. There are two issues that need to be addressed in applying discounts to the study outcome. Firstly, is whether to discount only the cost of the treatment or both cost and benefit of treatment. Secondly, is the amount of discount rate that will be applied in the study.

Although discounting both cost and benefit at the same rate was widely accepted in cost-benefit analysis, the use of the same discounting rate in cost-effectiveness analysis had recently come under criticism. The main argument for this was that unlike wealth, health cannot be invested to produce future gains (Sheldon, 1992).

Because of this, some guidelines recommended that health benefits should not be discounted (Drummond, 1994).

The present study will follow this recommendation by applying the recommended 3% discounting rate on the cost only in the baseline analysis (Drummond and McGuire, 2001).

Model Execution

The sample size for a Monte Carlo simulation needs to be large enough to reduce the variability in the sample means estimate (Drummond and McGuire, 2001).

A hypothetical sample of 10,000 patients will therefore be selected for simulation using Markov Monte Carlo model. The patients will be simulated individually at each iteration until the predetermined time horizon is reached (three years, five years, ten years and lifetime).

Analysis

The component cost i.e. outpatients and antiretroviral cost and QALY of PHAART and NHAART will be estimated at three years, five years, ten years and at the lifetime horizon. Incremental Cost-effectiveness Ratio (ICER) will then be calculated in terms of cost per QALY and cost per LY.

$$ICER = (C_T - C_C) / (E_T - E_C)$$

Where

C_T = Mean cost for PHAART group.

C_C = Mean cost for NHAART group.

E_T = QALY or LY in PHAART group.

E_C = QALY or LY in NHAART group.

ICER summarizes the trade-off between cost and effectiveness of compared choices. If this ICER is less than the willingness to pay or cost-effectiveness threshold, the treatment is considered cost-effective.

There are several ways to represent this decision rule. It can either be decided deterministically on the value, or using a cost-effectiveness plane that represents the threshold as a straight line that passes through the origin with the slope equal to the threshold (Figure 2.2) (Drummond and McGuire, 2001). Points underneath the threshold line indicate the cost-effectiveness of the interventions while above it indicates it is less cost-effective.

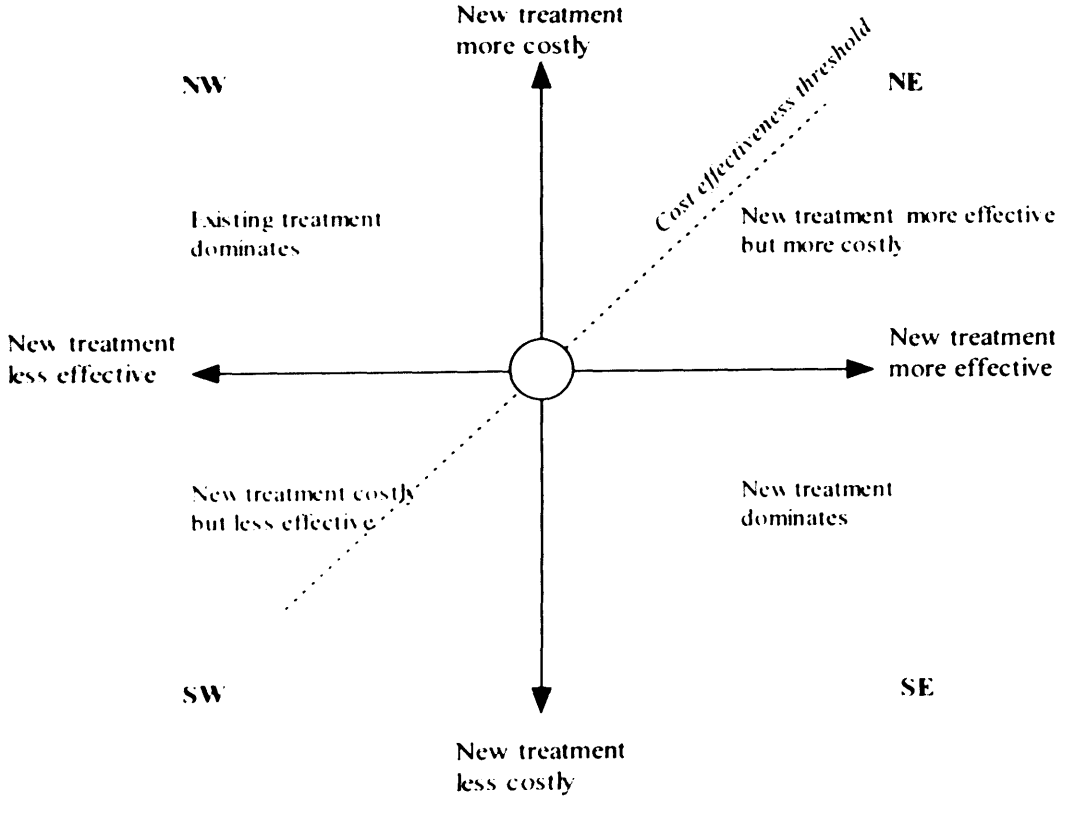


Figure 2.2 Cost-effectiveness plane (adapted from Drummond (2001))

Any uncertainty in this result which could arise in this analysis from the natural variation in populations and also the heterogenous external data source used, will be handled in two ways (Drummond and McGuire, 2001). Firstly, one way sensitivity analysis, which involves varying one parameter while holding others fixed will be conducted on the variable values of cost, discount (5%) and effectiveness (utility score and survival from existing literature). Secondly, a cost-effectiveness acceptability curve (CEAC) will be plotted to provide graphical representation of the probability that a particular intervention is optimal, over a range of values of willingness to pay or cost-effectiveness threshold (Fenwick et al., 2001).

SUMMARY

- HIV management has progressed rapidly and currently includes complex monitoring and treatment regimes that improve survival and reduce morbidity of HIV patients. This has resulted in a change in HIV natural history from acutely fatal to a chronic state disease.
- The complex management carries varying and multifaceted degrees of impact on clinical, economic and humanistic outcomes.
- The growing epidemic of HIV and issues of resource scarcity provides an impetus for investigating the impact on the economic framework.
- The present study consists of four sub studies that seek to investigate the longitudinal impact of initial HAART regimens on the cost and quality of life of HIV patients.
- These followed by exploratory modelling work of the observations into a longer time horizon.

Chapter 3

Study I: Resource Utilization and Cost Analysis

INTRODUCTION

HAART drastically changed the nature of HIV infection from a fatally acute to a chronic syndrome. These changes translate into a higher chronic care cost (outpatient and medication) than acute care (inpatient admission) compared to the pre HAART era (Beck et al., 2001). Furthermore, HAART itself and a new understanding of the pathology of HIV brought a myriad of complexities to the management of HIV patients. Different HAART regimens are known not only to differ in their efficacy, and safety profile, but also in their vulnerability to HIV resistance. Development of HIV resistance could in turn lead to cross resistance whereby the virus would not only be resistant to drug A, but also to any drug in the same class. This is especially profound in the NNRTI class where it was found that viral resistance towards nevirapine could induced resistance towards efavirenz as well (Antinori et al., 2002). These interactions between a myriad of clinical variables nevertheless brought significant economic implications for health cost payers as the combination of longer patient's life expectancy and new case incidences led to a higher prevalence of patients - hence the need for better understanding of cost information to make an informed budget allocation strategy.

Unfortunately, although a number of cost analyses of HIV infection have been done, a valid comparison of the studies for local use is made difficult by the heterogeneous design and lack of transparency of cost studies. The primary objective of this part of the study was to explore the effect of choice of initial treatment regimens on outpatient care costs. This study also explored other factors affecting the monthly cost for HIV patients seen between 1996 until end of 2005 and estimates the chronic cost per patient per month.

METHODS

Study Designs

This study was performed as a longitudinal retrospective study. All patients' that consented to the study between November 2004 and December 2005 were included.

Health resource utilization records were retrospectively collected between January 1996 to December 2005, from the time the patient were seen in either University Hospital of Wales or Cardiff Royal Infirmary outpatient care. These were collected until the time the patient left the study, were lost to follow-up, died or when the study ended.

Sample Size Estimation

The number of subjects needed per group, *m* was determined as detailed in Chapter 2. For the 80% (*P*) power of detecting cost difference between monthly times of 120 months (*n*), at the level of 5% significance (α), the number needed per group according to correlation, ρ and percentage difference was as in Table 3.1. Therefore, the number of needed subjects per group was to be at least 29 patients for the study intended duration, but will increase with high correlation among the repeated observations.

Table 3.1 Sample size needed per group for selected values of correlation, ρ and smallest meaningful difference in standard deviation unit, Δ

	Δ	
ρ	20%	30%
0.2	63.57	28.25
0.5	155.82	69.25

Ethics Approval

Ethics approval was issued by the South East Wales Research Ethics Committee (see Appendix I).

Description of Clinical Setting

The HIV clinics in both the University Hospital of Wales and Cardiff Royal Infirmary are an integrated service made up from multiple discipline staff. There is at least one consultant with either a specialist registrar or another consultant attending clinic at any one time. Other staffs in the team included an HIV specialist pharmacist, HIV specialist dietitian, HIV specialist nurse, phlebotomist, and a social worker.

Data Collection

Information on patients' resource utilization was collected retrospectively from their medical records from the health institutions perspective. The resources accounted for were: outpatient clinic visits; laboratory tests; imaging; and medical procedures. Other variables recorded for analysis included: risk factors; employment status; gender; nationality; antiretroviral treatment; viral load; CD4+ count; and HIV stage.

Costing

Total health resources used and costs were calculated for each patient as in Table 3.2. Because of the nature of file keeping in HIV clinics, whereby only clinical activity occurring in the respective HIV clinic is recorded, this study would be restricted to include only the activity occurring directly in the clinic.

Table 3.2 Itemized resource utilization and costing

ITEM	MEASUREMENT	DATA SOURCE	VALUATION
Radiography	Number of sessions	Medical Chart	Radiography Cost per Patient = Number of sessions X Radiography Cost per Session
Haematology Laboratory	Number of test	Medical Chart	Laboratory Cost per Patient = Number of test X Laboratory Cost per Test
Biochemistry Laboratory	Number of test	Medical Chart	Laboratory Cost per Patient = Number of test X Laboratory Cost per Test
Microbiology Laboratory	Number of test	Medical Chart	Laboratory Cost per Patient = Number of test X Laboratory Cost per Test
Resistance test	Number of test	Medical Chart	Laboratory Cost per Patient = Number of test X Laboratory Cost per Test
Radiography	Number of test	Medical Chart	Laboratory Cost per Patient = Number of test X Laboratory Cost per Test
Outpatient clinic visit (OCV)	Number of OCV	Medical Chart	Outpatient Cost per Patient = Number of OCV X Outpatient Clinic Cost per Visit
Other Medical Procedure (OMP)	Number of OMP	Medical Chart	OMP Cost per Patient = Number of OMP x OMP Cost per OMP

The table identified specific outpatient care resources included in the cost analysis. Each resource item was valued by multiplying its measured quantity with its specific charge/tariff.

Outpatient clinic visit is defined as a patient visit to the HIV outpatient clinic with pre-booked appointments for which a consultant is clinically responsible whether they are present at the clinic or not. This definition is consistent with the NHS Costing Manual (Department of Health, 2005a).

Cost per outpatient clinic at HIV clinic according to NHS Reference Cost was given as £924.00. This is the national average cost for outpatient HIV clinic that also includes tests and procedures. As this approach is an aggregate value that ignores practice variation and hence the actual resource use, outpatient clinic visit cost was separately calculated based on the total resources in clinic and mean patient attendance between 2004 – 2005. The value of health resources used in an outpatient clinic was based on a previous UK based costing report (Netten and Curtis, 2006).

Laboratory cost valuation was based primarily on the data from a reference pricelist provided by personal communication with Cardiff and Vale NHS Trust (McDowell, 2004). In the case of specialized laboratory tests or procedures that were unavailable in-house, price lists from other providers were referred to (Department of Health, 2005b, Newcastle Upon Tyne Hospitals NHS Trust, 2006, The University College London Hospital NHS Foundation Trust, 2005)

Analysis

Data were analyzed using STATA Intercooler 9.1. The study dataset was first transformed and conditioned for statistical purpose and better interpretation. This was done through the following means:

- Initially, the data was divided into monthly time increments with costs assigned to the month in which they were accrued.
- Viral load and CD4+ count measurement frequency could vary greatly among patients across time. Where there were multiple measurements of surrogate markers (CD4+ count and viral load) in a month, arithmetic mean were taken.
- In order to reduce skewness and heteroskedasticity, the natural logarithm of monthly cost was taken as dependent variable (Wooldridge, 1999).
- Age was centred on mean of 40 years old for better interpretation of results (Singer and Willett, 2003). For example, without recentering, intercept in the level one submodel, π_{0i} would give the true value of Y at age 0. Recentering at grand mean would allow the value to represents the average fitted values of initial status.
- Dummy variables, with only values of zero or one, were created for categorical variables with more than two levels.

Table 3.3 gives full description of the variables transformation included in the analysis.

Descriptive

Descriptive demographic, clinical and cost distribution were tabulated and analyzed for background of the study samples. This was followed by a longitudinal exploratory data analyses to identify important features in the dataset and prepare for subsequent model-based analysis. For ease of analysis, the first twelve patients' empirical monthly cost trajectory was graphically summarized using non parametric

lowess smoothing to assess within individual change without specifying any functional form.

Table 3.3 Codebook for variables collected and included in the analysis

	Description	Variables Name	Note
Y	Outpatient care monthly cost	lncost	Natural log of outpatient care monthly cost
X1	Age of patient	age	Age – grand mean (40)
X2	Primary outpatient care clinic	loc	1=Cardiff Royal Infirmary;0=University Hospital of Wales
X3	Factors associated with increased risk for HIV transmission	rf1	1=homosexual; 0=other
X4		rf2	1=intravenous drug user;0=other
X5	Employment status on recruitment	emp1	1=employed;0=other
X6		emp2	1=pensioner;0=other
X7		emp3	1=student;0=other
X8		emp4	1=unemployed;0=other
X9	Gender	gender1	1=female;0=other
X10		gender2	1=male;0=other
X11	Nationality on recruitment	nat	1=british;0=other
X12	Initial antiretroviral regimen	initreg1	1=PHAART;0=other
X13		initreg2	1=NHAART;0=other
X14		initreg3	1=non HAART, no treatment;0=other
X15	Antiretroviral regimen at time *j*	curreg1	1=PHAART;0=other
X16		curreg2	1=NHAART;0=other
X17		curreg3	1= non HAART, no treatment;0=other
X18	Stage of HIV infection at time *j*	hivstage1	1=non AIDS;0=other
X19		hivstage2	1=AIDS;0=other
X20	Ethnicity of patient	ethn1	1=white;0=other
X21		ethn2	1=black;0=other
X22		ethn3	1=asian;0=other
X23		ethn4	1=mixed;0=other
X24	Categorization of viral load at time *j*	vlcat1	1=<1000;0=other
X25		vlcat2	1=>1000;0=other
X26	Categorization of CD4+ count at time *j*	cd4cat1	1=<250;0=other
X27		cd4cat2	1=250-500;0=other
X28		cd4cat3	1=>500;0=other
X29	Time in monthly unit	time	

This enables analysis of individual patterns of change over time and also informs the functional form of the trajectory. The monthly cost was later fitted linearly according

to their demographic categories to assess change at level two of multilevel model i.e. across people.

Multilevel Model of Change in Cost

The longitudinal nature of the study would enable answering the thesis question of the influence of initial treatment on the changes of monthly chronic cost over time while controlling for other clinical and demographic covariates.

This was done using multilevel model method whereby it could address two types of questions in the analysis of change:

1. *Within individual change*: How does each patient's monthly cost change over time?
2. *Interindividual differences in change*: What predicts differences among patients in their changes?

Multilevel model addresses question one as a level one submodel that describes how individual changes over time and question two as a level two submodel that describes how these changes vary across individuals. This can be formulated as in the following equation:

$$Y_{ij} = \pi_{0i} + \pi_{1i} X_{ij} + e_{ij} \qquad \textit{Level One}$$

where

$$\pi_{0i} = \gamma_{00} + \gamma_{01} Z_i + \zeta_{0i} \qquad \textit{Level Two}$$
$$\pi_{1i} = \gamma_{10} + \gamma_{11} Z_i + \zeta_{1i}$$

In other words, the model could be considered as a nested structure with the occasions of measurement defining level one and the individuals defining level two. Taking both together in one composite model gives name to a form known as multilevel statistical model which is summarized in the following equation:

$$Y_{ij} = [\gamma_{00} + \gamma_{01}Z_{1i} + \gamma_{10}X_{1ij} + \gamma_{11}Z_{1i}X_{1ij}] + [\zeta_{oi} + \zeta_{1i}X_{1ij} + e_{ij}]$$

Where:

Y_{ij}	The value for patient i at time j.
π_{0i}	Intercept of the true change trajectory for individual i in the population.
π_{1i}	Slope of the true change trajectory for individual i in the population.
e_{ij}	Random measurement error at level one
γ_{00}	Population average of the level one intercepts, π_{0i} for individuals with a level two predictor value of 0.
γ_{01}	Population average difference in level one intercept, π_{0i}, for a 1-unit difference in the level two predictor.
γ_{10}	Population average of the level one slopes, π_{1i} for individuals with a level two predictor value of 0.
γ_{11}	Population average difference in level one slope, π_{1i} for a 1-unit difference in the level two predictor.
Z_{1i}	Level two predictor for patient i.

Model Specification

i) Level One

Based on the above formula, to see whether the monthly cost differs systematically with time for each patient, a Simple Linear Model for Individual Change at level one was specified as:

$$lncost_{ij} = \pi_{0i} + \pi_{1i}(time_{ij}) + e_{ij}$$

Where

lncost	Natural log of outpatient care monthly cost
time	Time in monthly unit

In multilevel model of change, time varying (TV) variable was modelled in level one. Therefore, the following equation postulates all possible level one variables in a linear equation.

$$lncost_{ij} = \begin{pmatrix} \pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(age_{ij}) + \pi_{3i}(cd4cat1_{ij}) + \pi_{4i}(cd4cat2_{ij}) + \\ \pi_{5i}(vlcat1_{ij}) + \pi_{6i}(curreg1_{ij}) + \pi_{7i}(curreg2_{ij}) + \pi_{9i}(initreg1_{ij}) + \\ \pi_{10i}(initreg2_{ij}) + \pi_{11i}(initreg3_{ij}) + \pi_{12i}(hivstage2_{ij}) + e_{ij} \end{pmatrix}$$

Where

lncost	Natural log of outpatient care monthly cost
time	Time in monthly unit
age	Age of patient
cd4cat	Categorization of CD4+ count at time j
vlcat	Categorization of viral load at time j
curreg	Antiretroviral regimen at time j
initreg	Initial antiretroviral regimen
hivstage	Stage of HIV infection at time j

ii) Level Two

Variables included as level two were gender, location of outpatient care, ethnicity, nationality, and employment. The taxonomy of postulated models with level one, level two and composite specification are summarized in Table 3.4.

Modelling Strategy

The modelling strategy involved analyzing the postulated models (Table 3.4) based on the preliminary graphic observation that included model specification and how they were related to the level one and level two specification.

Table 3.4 Taxonomy of fitted model for level one (continue next page)

MODEL	LEVEL	SPECIFICATION
A: Unconditional Means Model	Level 1; $lncost_{ij}$ =	$\pi_{0i} + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{00} + \zeta_{0i}$
	Composite; $lncost_{ij}$ =	$\gamma_{00} + \zeta_{0i} + e_{ij}$
B: Unconditional Growth Model	Level 1; $lncost_{ij}$ =	$\pi_{0i} + \pi_{1i}(time_{ij}) + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{00} + \zeta_{0i}$; $\pi_{1i} = \gamma_{10} + \zeta_{1i}$
	Composite; $lncost_{ij}$ =	$\gamma_{00} + \gamma_{10}(time_{ij}) + \zeta_{0i} + \zeta_{1i}(time_{ij}) + e_{ij}$
C1: Adding the main effect of time varying predictors. (Initial treatment regimen)	Level 1; $lncost_{ij}$ =	$\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(initreg1_{ij}) + \pi_{3i}(initreg2_{ij})$
	Level Two	$\pi_{0i} = \gamma_{01} + \zeta_{0i}$; $\pi_{1i} = \gamma_{10} + \zeta_{1i}$; $\pi_{2i} = \gamma_{20}$; $\pi_{3i} = \gamma_{30}$
	Composite	$(\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(initreg1_{ij}) + \gamma_{30}(initreg2_{ij})) + (\zeta_{0i} + \zeta_{1i}(time_{ij}) + e_{ij})$
C2: Adding the main effect of time varying predictors. (age)	Level 1; $lncost_{ij}$ =	$\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(initreg1_{ij}) + \pi_{3i}(initreg2_{ij}) + \pi_{4i}(age_{ij}) + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{01} + \zeta_{0i}$; $\pi_{1i} = \gamma_{10} + \zeta_{1i}$; $\pi_{2i} = \gamma_{20}$; $\pi_{3i} = \gamma_{30}$; $\pi_{4i} = \gamma_{40} + \zeta_{4i}$;
	Composite $lncost_{ij}$ =	$(\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(initreg1_{ij}) + \gamma_{30}(initreg2_{ij}) + +\gamma_{40}(age_{ij})) + (\zeta_{0i} + \zeta_{1i}(time_{ij}) + \zeta_{4i}(age_{ij}) + \zeta_{ij} + e_{ij})$

Key: *lncost* = natural log of outpatient care monthly cost, *time* = time in monthly unit, *initreg* = initial antiretroviral regimen, *age* = age of patient

Table 3.4 Taxonomy of fitted model (cont. 2).

C3: Adding the main effect of time varying predictors. (HIV Stage)	Level 1; $lncost_{ij}$ =	$\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(initreg1_{ij}) + \pi_{3i}(initreg2_{ij}) + \pi_{4i}(age_{ij}) + \pi_{5i}(cd4cat1_{ij}) + \pi_{6i}(cd4cat2_{ij}) + \pi_{7i}(vlcat2_{ij}) + \pi_{8i}(hivstage2_{ij}) + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{01} + \zeta_{0i}$; $\pi_{1i} = \gamma_{10} + \zeta_{1i}$; $\pi_{2i} = \gamma_{20}$; $\pi_{3i} = \gamma_{30}$; $\pi_{4i} = \gamma_{40}$; $\pi_{5i} = \gamma_{50}$; $\pi_{6i} = \gamma_{60}$; $\pi_{7i} = \gamma_{70}$; $\pi_{8i} = \gamma_{80} + \zeta_{8i}$
	Composite $lncost_{ij}$ =	$\left(\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(initreg1_{ij}) + \gamma_{30}initreg2_{ij}) + \gamma_{40}(age_{ij}) + \gamma_{50}(cd4cat1_{ij}) + \gamma_{60}(cd4cat2_{ij}) + \gamma_{70}(vlcat2_{ij}) + \gamma_{80}(hivstage2_{ij})\right) + \left(\zeta_{1i}(time_{ij}) + \zeta_{8i}(hivstage2_{ij}) + \zeta_{0i} + e_{ij}\right)$
C4: Adding the main effect of time varying predictors. (Current Regimen)	Level 1; $lncost_{ij}$ =	$\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(initreg1_{ij}) + \pi_{3i}(initreg2_{ij}) + \pi_{4i}(age_{ij}) + \pi_{5i}(cd4cat1_{ij}) + \pi_{6i}(cd4cat2_{ij}) + \pi_{7i}(vlcat2_{ij}) + \pi_{8i}(hivstage2_{ij}) + \pi_{9i}(curreg1_{ij}) + \pi_{10i}(curreg2_{ij}) + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{01} + \zeta_{0i}$; $\pi_{1i} = \gamma_{10} + \zeta_{1i}$; $\pi_{2i} = \gamma_{20}$; $\pi_{3i} = \gamma_{30}$; $\pi_{4i} = \gamma_{40}$; $\pi_{5i} = \gamma_{50}$; $\pi_{6i} = \gamma_{60}$; $\pi_{7i} = \gamma_{70}$; $\pi_{8i} = \gamma_{80} + \zeta_{8i}$; $\pi_{9i} = \gamma_{90} + \zeta_{9i}$; $\pi_{10i} = \gamma_{100}$
	Composite $lncost_{ij}$ =	$\left(\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(initreg1_{ij}) + \gamma_{30}initreg2_{ij}) + \gamma_{40}(age_{ij}) + \gamma_{50}(cd4cat1_{ij}) + \gamma_{60}(cd4cat2_{ij}) + \gamma_{70}(vlcat2_{ij}) + \gamma_{80}(hivstage2_{ij}) + \gamma_{90}(curreg1_{ij}) + \gamma_{100}(curreg2_{ij})\right) + \left(\zeta_{1i}(time_{ij}) + \zeta_{8i}(hivstage2_{ij}) + \zeta_{0i} + e_{ij}\right)$

Key: *lncost* = natural log of outpatient care monthly cost, *time* = time in monthly unit, *initreg* = initial antiretroviral regimen, *age* = age of patient, *curreg* = antiretroviral regimen at time *j*, *hivstage* = stage of HIV infection at time *j*, *cd4cat* = categorization of CD4+ count at time *j*, *vlcat* = categorization of viral load at time *j*

Intraclass correlation and proportion of explained outcome variation were first estimated using the unconditional means model and the unconditional growth model (Model A and B in Table 3.4). Model was fitted for variable in level one first, before proceeding to level two model fitting with the best fitted level one model. Model was selected using single parameter *t*-statistics and Wald statistics for overall model comparison.

Missing Values

Some variables such as stages of HIV infection were not regularly recorded in patient's medical records. This data would be imputed by cross referencing to patient records and manually assessing patient's stage according to the Centre for Disease Control Clinical Staging System for HIV (Centre for Disease Control and Prevention, 1992). In this system, HIV infection is clinically categorized into asymptomatic, symptomatic and AIDS based on the development of predefined specific symptom or diagnosis. The assignment of categories is performed on a mutually exclusive basis where the most advanced category designation remains once the end point is reached i.e. patients cannot improve their assigned clinical category but can only advance to subsequent categories.

Other missing covariates were managed using multiple imputation that replace missing values with 'plausible' substitutes based on distribution of given data and a small amount of randomness in the imputation model. This was implemented in STATA's *ice* module. Details of this approach were given in 'Study Plan, Data Processing and Analysis' section in Chapter 2.

The general syntax for multiple imputations in this module is:

```
ice mainvarlist using filename[.dta], cmd(cmdlist) m(#)
```

The imputation model for the missing values was specified according to the type of variables. Ordinal logistic regression was used in the prediction model for missing data in categories of viral load and CD34 as the categories are ordered by their severity. This was specified in the *cmd* option in the *ice* module. Other unordered categorical variables including employment, risk factor and nationality were predicted by multinomial logistic regression model. Full syntax implementation of the imputation in STATA was outlined in Appendix VIII.

RESULTS

A total of 150 patients were recruited between November 2004 and 31st December 2005. 100 patients (66.67%) were recruited from Cardiff Royal Infirmary while the rest were from the University Hospital of Wales. The total number of patients seen in Cardiff Royal Infirmary during this period was 257 patients. It was not possible however to determine the number of HIV patients seen in the UHW clinic, as the clinic was attended by non HIV patients as well. A total of 4,306 observations were collected from this sample between 1st January 1996 and 31st December 2005. Details of the study dataset integrity were given in Figure 3.1.

Sociodemographic Characteristics

Patients included were as young as 16 years old with the oldest being 71 years old (Table 3.5). The mean age was 39.7 years. The mean SD between patients was 9.9 years while SD for the same patients across the time line was 2.2 years. Patients were mostly male (n_{male}=125; 83.3%) with white constituting the majority ethnicity of all patients (n_{white}=116; 77.3%). British nationals made up 76.7% of all patients whilst

African were the biggest non British nationality among patients ($n_{African}$=20; 13.3%). 67 patients (44.7%) were employed on recruitment.

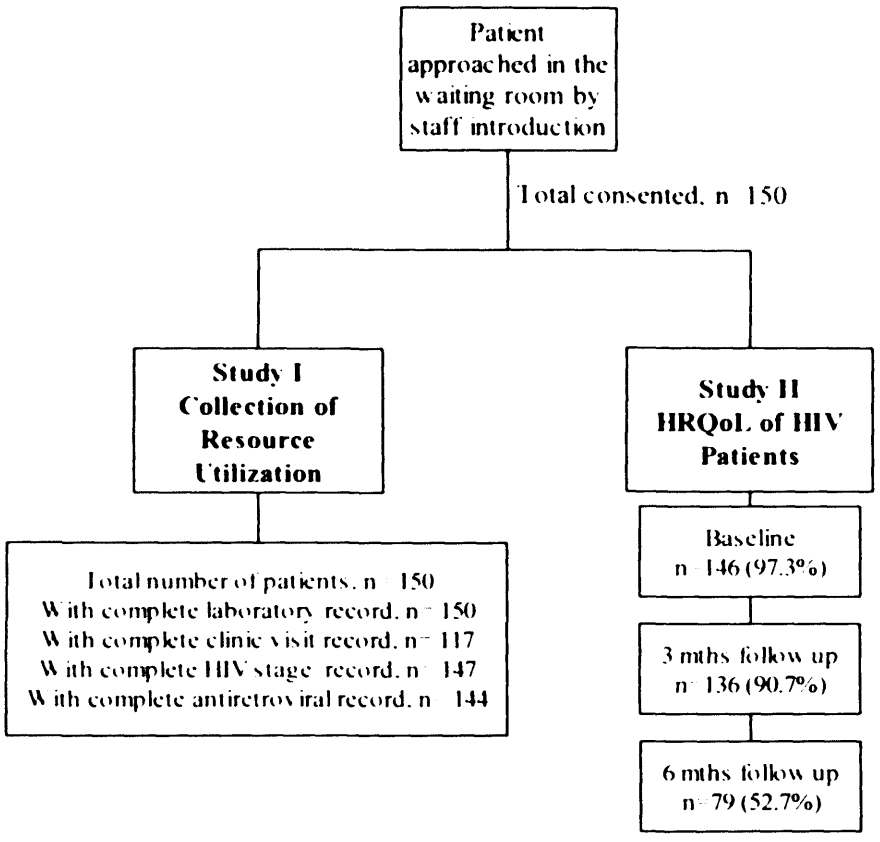


Figure 3.1 Diagram of study design and data completion

Clinical Parameters

The mean CD4+ count for patients was 384.2 cells/mm^3 (SD=248.7) and viral load was 3.81E+05 copies/mL (SD=1.72E+06) (Table 3.6). 62.7% of patients were homosexual while the rest were heterosexual (n_{hetero}=45; 30.0%), intravenous drug users (n_{IVDU}=5; 3.2%), and transfusion patients ($n_{transfusion}$=1; 0.7%). At initial time (when patient first accrued cost), 74 of patients were asymptomatic (51.0%), 47 were symptomatic (32.4%) and 24 were already diagnosed as in AIDS stage (16.6%).

Table 3.5 Sociodemographic characteristics (n = 150)

Variable		Mean	Std. Dev.	Min	Max	Observations
Age	overall	39.72	10.00	16.00	71.00	N = 4306
	between		9.89	17.00	66.28	n = 150
	within		2.18	32.98	45.10	T-bar = 28.7067

Variable	Overall		Between		Within
	Freq.	%	Freq.	%	%
GENDER					
Female	578	13.42	25	16.67	100
Male	3728	86.58	125	83.33	100
Total	4306	100	150	100	100
ETHNICITY					
White	3724	86.48	116	77.33	100
Black	368	8.55	22	14.67	100
Asian	111	2.58	2	1.33	100
Mixed	103	2.39	4	2.67	100
Total	4306	100	144	96	100
NATIONALITY					
British	3635	87.19	115	76.67	100
African	293	7.03	20	13.33	100
American	73	1.75	2	1.33	100
Asian	38	0.91	1	0.67	100
Other EU	130	3.12	6	4.00	100
Total	4169	100	144	96	100
EMPLOYMENT					
Employed	1756	42.22	67	44.67	100
Pensioner	138	3.32	5	3.33	100
Student	75	1.8	4	2.67	100
Unemployed	2190	52.66	66	44.00	100
Total	4159	100	142	94.67	100
LOCATION					
CRI	3128	72.64	100	66.67	100
UHW	1178	27.36	50	33.33	100
Total	4306	100	150	100	100

There were 29 distinct combinations of antiretroviral regimens initially received by patients as their first line treatment (Figure 3.2). The top three initial regimens consist of efavirenz (EFV), lamivudine (3TC) and zidovudine (AZT) (29.6%); nevirapine (NVP), 3TC and AZT (15.3%); EFV, emcitrabine (FTC) and tenofovir (TDF) (8.2%). Grouping them into their pharmacological combinations shows that 73.3% were on NHAART regimens.

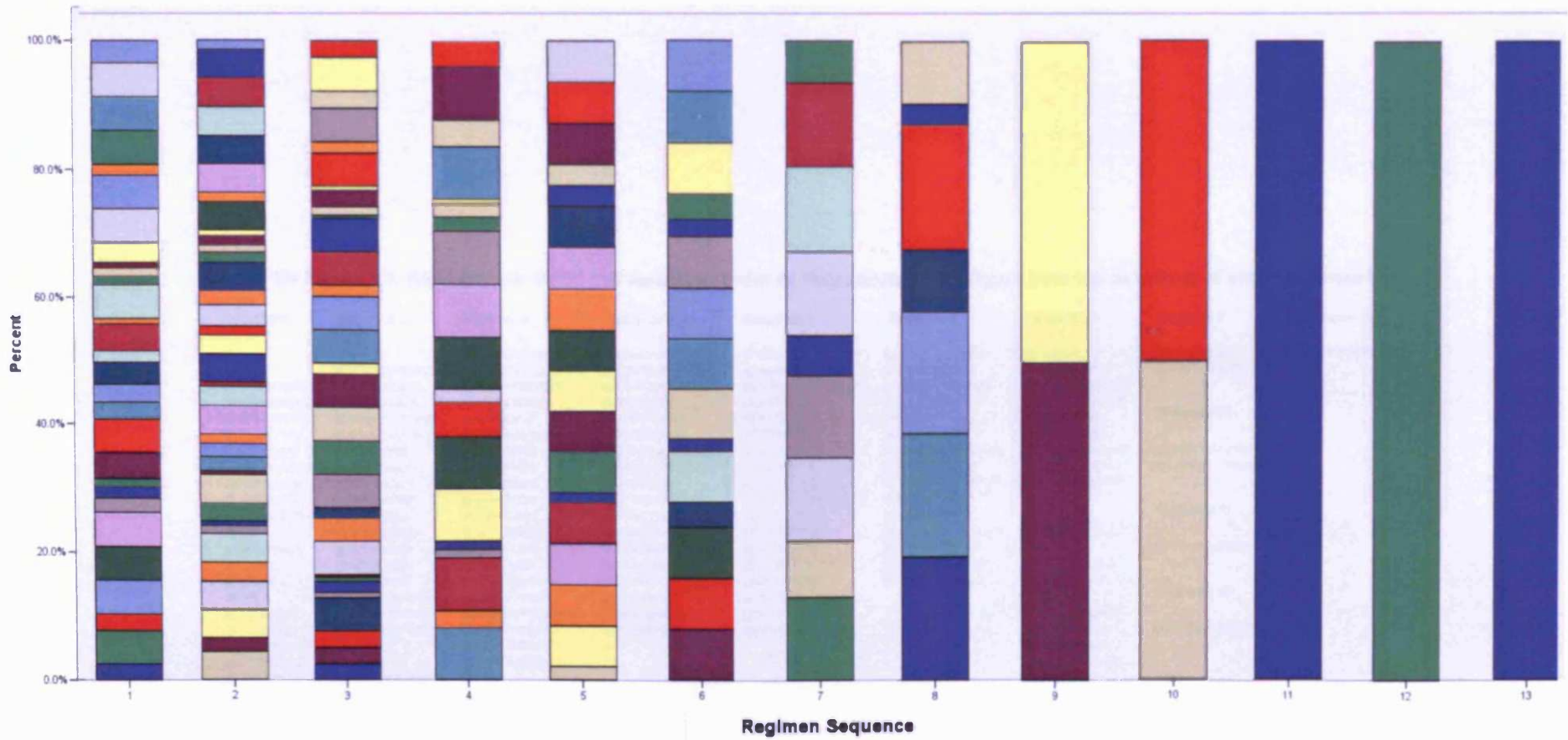


Figure 3.2 Percentage of antiretroviral regimen combinations at each regimen sequence beginning from the first treatment initiation (figure legend on next page)

Legend for Figure 3.2. Regimens are listed in descending order as they appear in the figure from top to bottom of each sequence bar

Key: 3TC = Lamivudine, ABC = Abacavir, ATV = Atazanivir, AZT = Zidovudine, D4T = Stavudine, DDI = Didanosine, EFV = Efavirenz, FTC = Emcitrabine, IDV = Indinavir, LPV = Lopinavir, RTV = Ritonavir, SQV = Saquinavir, T20 = Enfuvirtide, TDF = Tenofovir, TPV = Tipranavir

Table 3.6 Clinical distribution

Variable		Mean	Std. Dev.	Min	Max	Observations
CD4+	overall	384.17	248.67	0.00	1880.00	N = 4225
	between		192.34	66.92	1059.17	n = 150
	within		158.01	-129.06	1683.00	T-bar = 28.1667
Viral Load	overall	3.81E+05	1.44E+07	0.00E+00	6.50E+08	N = 4072
	between		1.72E+06	0.00E+00	2.10E+07	n = 150
	within		1.42E+07	-2.06E+07	6.29E+08	T-bar = 27.1467

Variable	Overall		Between		Within
	Freq.	%	Freq.	%	%
RISK FACTOR					
Heterosexual	1095	29.33	45	30.00	100
Homosexual	2452	65.67	94	62.67	100
Intravenous Drug User (IVDU)	166	4.45	4.8	3.200	100
Transfusion	21	0.56	1	0.67	100
Total	3734	100	147	98.00	100
CD4 CATEGORIES					
<250	1076	25.47			38.02
250-500	1995	47.22			49.17
>500	1154	27.31			37.52
Total	4225	100			42.66
VIRAL LOAD CATEGORIES					
<1000	2815	69.13			72.65
>1000	1257	30.87			35.45
Total	4072	100			54.05
HIV STAGE					
Asymptomatic	888	20.62			39.36
Symptomatic	2292	53.23			72.92
AIDS	1126	26.15			90.88
Total	4306	100			64.73
INITIAL TREATMENT REGIMEN					
PHAART	868	20.16	25	16.67	92.44
NHAART	1124	26.1	69	46.00	74
non HAART	1348	31.31	27	18.00	97.12
no ARV	966	22.43	20	13.33	35.55
Total	4306	100	141	94.00	61.23
CURRENT REGIMEN					
PHAART	1243	28.87			49.62
NHAART	1746	40.55			54.58
non HAART	133	3.09			10.64
no ARV	1184	27.5			35.67
Total	4306	100			42.98

Due to various clinical and preference reasons, patients initial regimen were changed several times with up to thirteen changes recorded in the present cohort.

Monetary Value of the Services

The cost per outpatient clinic visit was calculated and estimated as in Table 3.7. This gave the outpatient clinic visit cost as £152.61 per patient per visit. This estimate was multiplied by the number of outpatient clinic visit by the patient and combined with estimates from laboratory, imaging and procedure costs to give the total patient cost per month.

Table 3.7 Costing of outpatient clinic visit per patient

COSTING POOL	UNITS	COST/UNIT(£/hr)	TOTAL HOURS	COST/DAY
Nursing				
Spec nurse	hours a day	£37	6	£222
Staff nurse	hours a day	£23	6	£138
Doctor				
Consultant	hours a day	£73	6	£438
SpR	hours a day	£54	6	£324
Dietitian	hours a day	£23	6	£138
Pharmacist	hours a day	£28	6	£168
Social worker	hours a day	£25	6	£150
Total				£1,578
Mean Daily Total Patient Attendances				10.34
SD				3.06
Outpatient clinic visit/patient				£152.61

The monthly cost for each component is given in Table 3.8. Laboratory cost totaling £127.53 which included microbiology tests, haematology tests, biochemistry tests, genotyping tests, and therapeutic drug monitoring made up most of the monthly total cost (53.7%). This was followed by contribution from clinic visit cost that gave a total of £102.98 (43.3%). An imaging cost of £3.18 made up only 1.3% of the total costs

Table 3.8 Monthly cost of component and total cost (£)

Variable		Mean	Std. Dev.	Min	Max	Observations
Procedure	overall	1.83	32.03	0	1100	N = 4157
	between		7.51	0	70	n = 145
	within		31.33	-67.18	1085.88	T-bar = 28.67
Clinic Visit	overall	102.98	111.04	0	915.66	N = 4157
	between		78.33	0	281.74	n = 145
	within		80.79	-178.77	883.98	T-bar = 28.67
Laboratory	overall	127.53	82.24	0	708.35	N = 4157
	between		33.79	33.63	282.32	n = 145
	within		78.16	-154.79	649.25	T-bar = 28.67
Imaging	overall	3.18	20.77	0	487.43	N = 4157
	between		6.13	0	40.99	n = 145
	within		19.94	-37.81	469.25	T-bar = 28.67
Total Cost	overall	237.59	152.32	1.24	1301.01	N = 4157
	between		88.93	98.40	549.39	n = 145
	within		129.74	-133.94	1251.62	T-bar = 28.67

while procedure cost only added £1.83 (0.77%) to the total monthly outpatient costs per patient.

Longitudinal Exploratory Data Analysis

As with any data analysis, this study begins by making displays to expose the patterns relevant to the scientific questions before moving into a more complex statistical analysis. This was done by examining the relationship of the independent and dependent variables with time.

Examining Empirical Graph Plot for First Twelve Patients

The cost hovers on the top of the scale (Figure 3.3). Some patients (ID: 2, 7) had stable monthly costs over time but most other patients in this small sample had declining monthly costs with varying slope steepness.

This illustration demonstrated that monthly costs did change for each patient with different rates of change across people.

The overall impression from linearly fitted values suggested that costs increased with time with some variations in the fit (Figure 3.4). This indicates that a deeper analysis on this change was warranted.

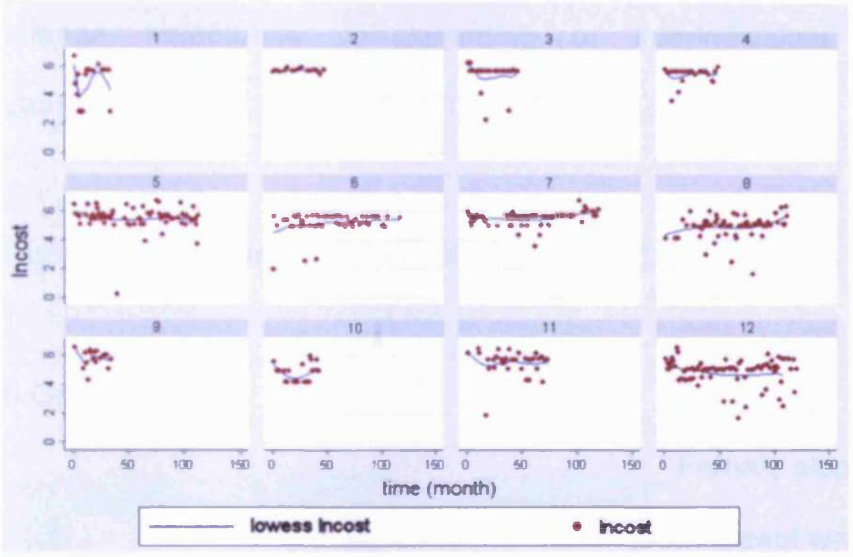


Figure 3.3 Smooth nonparametric summaries (lowess) of how the monthly cost in twelve individual patients change over time. Key: *lncost* = natural log of outpatient care monthly cost.

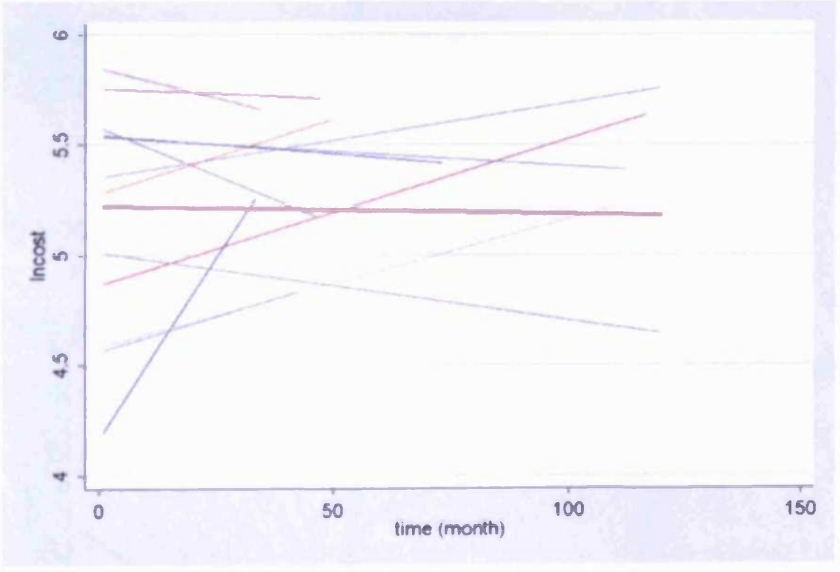


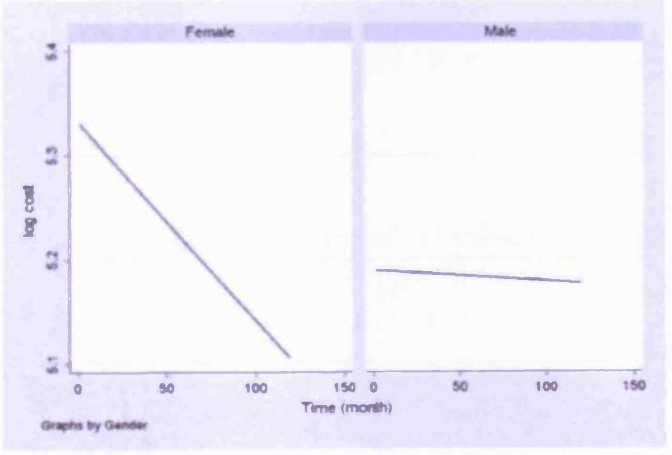
Figure 3.4 Linear fitted values of monthly cost for all patients in the study (n = 150) and twelve individual fitted trajectories. *Thick line represented the overall linear fitted values and the thin lines are the individual fitted values.*

Examining Factors Influencing Interindividual Differences

The whole 150 cohort was evaluated for the impact of time invariant predictors over time (Figure 3.5). This would help uncover systematic patterns in the individual change trajectories corresponding to interindividual variation in personal characteristics.

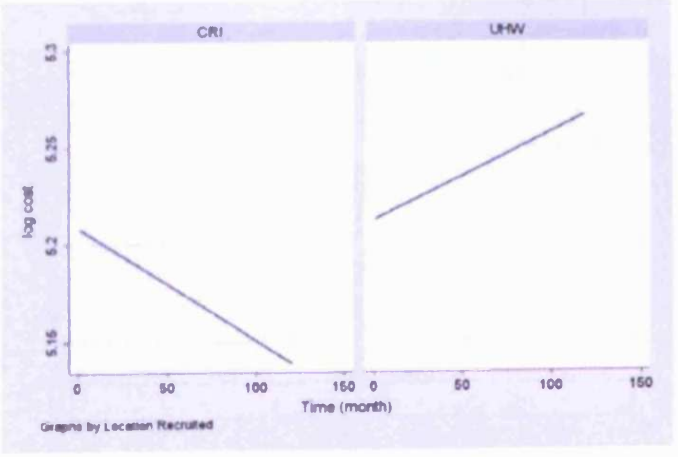
Figure 3.5 Linear prediction of log cost vs time

i) Gender



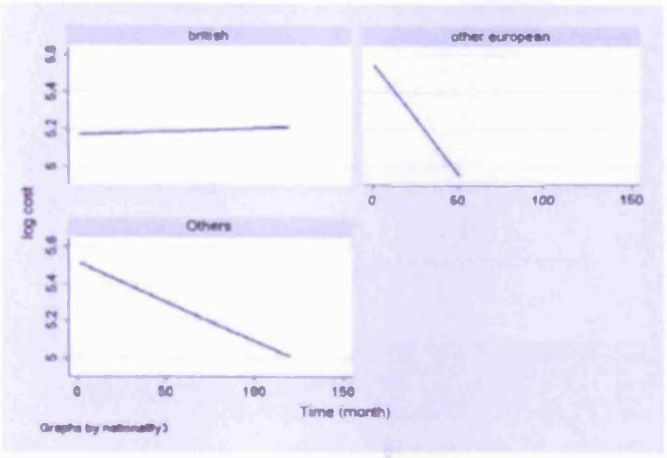
Female slope was much steeper and intercept was higher than male.

ii) Location



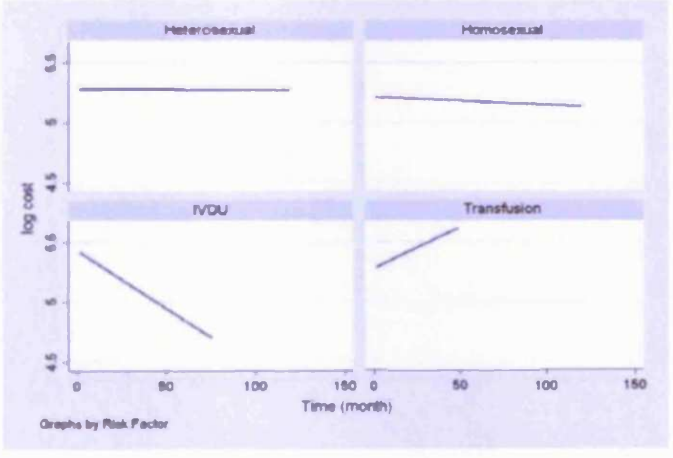
Intercept almost the same but CRI had negative slope vs UHW positive slope.

iii) Nationality



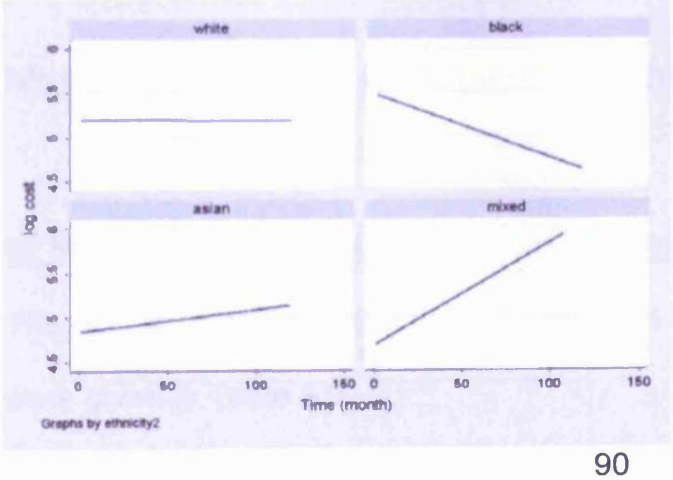
Intercept for non British was higher. Slope was also much steeper than British patients but with negative slope.

iv) Risk Factor



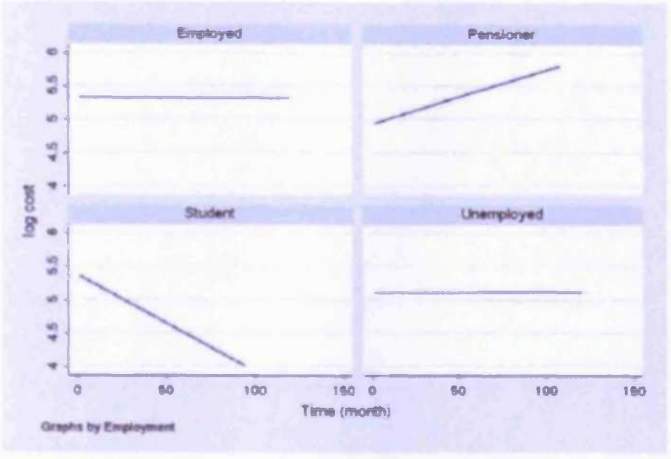
Intercept almost the same for all but slope differs. Intravenous drug user (IVDU) and transfusion slope was steeper than homosexual and heterosexual. Slope also negative for IVDU.

v) Ethnicity



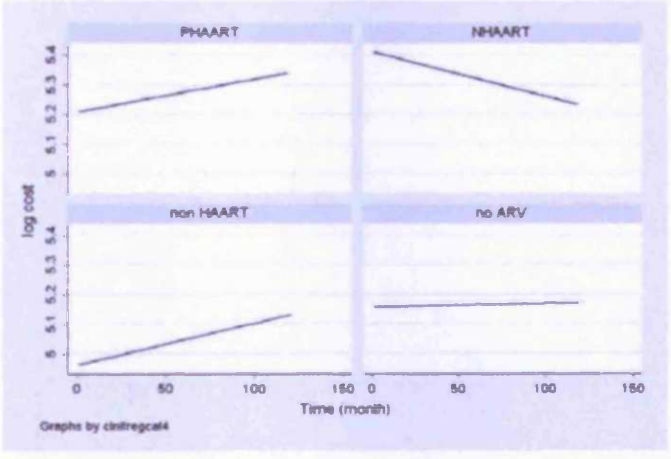
Intercept were much lower for Asian and mixed compared to white and black. Slope varied with white having the least steep slope. Black and white had negative slope.

vi) Employment



Intercept almost the same. But slope varied with student and pensioner steeper than employed and unemployed. Student slope was negative.

vi) Initial treatment regimens



Intercept varied. Non HAART had the lowest intercept followed by no ARV, PHAART and NHAART. Slope steepness almost the same for ARV receiving groups with NHAART having negative slope.

The results of exploratory analysis show the effect the predictors have on the cost of outpatient care. This would be further analyze in the following section.

Multilevel model of Change in Monthly Cost

a) Model Fitting and Comparison for Level 1 Submodel

The results of fitting multilevel model for level one variables as specified in Table 3.4 were given in Table 3.9.

Model A: The Unconditional Means Model

$$lncost_{ij} = \gamma_{(0)} + \zeta_{0i} + e_{ij}$$

The estimated mean of monthly cost across all time and individuals, γ_{00} was

$= e^{(5.258)}$

$= £192.10$

Rejection of its null hypothesis (p<0.001) confirms that this mean of monthly cost for average patients is non zero.

The main purpose of this model was to partition the variation in the model to two components, within person and initial status.

The variance for within individual, σ_e^2 and between person, σ_0^2 were both more than twice standard deviation indicating that the average monthly cost varied over time and that patients differ from each other in monthly cost (Singer and Willett, 2003). STATA however didn't provide single parameter hypothesis test for random effects in multiple imputed data.

The amount of variation between patients regardless of time was given by $\hat{\sigma}_e^2$ and the amount of variation within individuals over time was given by $\hat{\sigma}_0^2$.

Intraclass correlation (ICC) that would give the proportion of total variation in Y that lies between patients could then be calculated, given that

$$ICC = \frac{\sigma_0^2}{\sigma_0^2 + \sigma_e^2}$$

$$\therefore ICC = \frac{-0.969}{-0.969 - 0.251} = 0.794$$

This shows that an estimated 79.4% of the total variation in chronic care cost was attributable to differences between patients. It also means that for each patient, the average correlation between any pair of composite residuals was 0.794. This clearly violates the zero residual autocorrelation assumption that is required in an ordinary least square (OLS) analysis.

So, what role did TIME play? This was evaluated in model B.

Model B: The Unconditional Growth Model

$$lncost_{ij} = \gamma_{00} + \gamma_{10}(time_{ij}) + \zeta_{0i} + \zeta_{1i}\left(time_{ij}\right) + e_{ij}$$

The average true change trajectory for monthly cost, γ_{10} was estimated to be 5.185 (p<0.001). The slope ζ_{1i} was not significant. However, in order to analyze the relation of time with other predictors, time variables would be preserved in the model.

Model C1: Inclusion of initial treatment regimens

$$lncost_{ij} = \left[\begin{array}{l}\left(\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(initreg1_{ij}) + \gamma_{30}initreg2_{ij})\right) + \\ \left(\zeta_{1i}(time_{ij}) + \zeta_{0i} + e_{ij}\right)\end{array}\right]$$

The parameter estimate of TIME (*time)*, γ_{10} was still not statistically significant (Table 3.9). However, initial treatment regimens had a statistically significant effect on the monthly cost (p<0.10) whereby the average monthly cost was 15.4% higher in patient's with PHAART initial regimen and 9.6% higher in patient with NHAART initial regimen.

Model C2: Inclusion of Age into C1

$$lncost_{ij} = \left[\begin{pmatrix} \gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(initreg1_{ij}) + \gamma_{30}(initreg2_{ij}) + \\ \gamma_{40}(age_{ij}) \end{pmatrix} + \begin{pmatrix} \zeta_{1i}(time_{ij}) + \zeta_{4i}(age_{ij}) + \zeta_{0i} + e_{ij} \end{pmatrix} \right]$$

lncost	Natural log of outpatient care monthly cost
time	Time in monthly unit
age	Age of patient
initreg	Initial antiretroviral regimen

Model C2 evaluates the effect on monthly cost by age while controlling for initial regimen and time. All parameters were statistically significant (p<0.05).

Model C3: Inclusion of Markers (CD4+ count and viral load) and HIV Stage into C2

$$lncost_{ij} = \left[\begin{pmatrix} \gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(initreg1_{ij}) + \gamma_{30}(initreg2_{ij}) + \\ \gamma_{40}(age_{ij}) + \gamma_{50}(cd4cat1_{ij}) + \gamma_{60}(cd4cat2_{ij}) + \\ \gamma_{70}(vlcat2_{ij}) + \gamma_{80}(hivstage2_{ij}) \end{pmatrix} + \begin{pmatrix} \zeta_{1i}(time_{ij}) + \zeta_{8i}(hivstage2_{ij}) + \zeta_{0i} + e_{ij} \end{pmatrix} \right]$$

where

lncost	Natural log of outpatient care monthly cost
time	Time in monthly unit
age	Age of patient
cd4cat1	Categorization of CD4+ count <250 cells/mm^3 at time j
cd4cat2	Categorization of CD4+ count 250 – 500 cells/mm^3 at time j
vlcat1	Categorization of viral load < 1000 at time j
initreg1	Initial antiretroviral regimen with PHAART
initreg2	Initial antiretroviral regimen with NHAART
hivstage2	Stage of HIV infection (AIDS) at time j

Evaluating the effect of markers while controlling for time, initial regimen, and age on the monthly cost gave a statistically significant hypothesis test of non zero for all parameters (p<0.01). Therefore, model C3 gave the best fitted level one model for the sample. This model would provide the basis for the level two model specification in the next section.

b) Model Fitting and Comparison for Level Two

Results for adding level-2 variables into best fitted level one models are given in Table 3.10. Only level two variables of nationality intercept gave a statistically significant non zero effect on monthly cost (p<0.05).

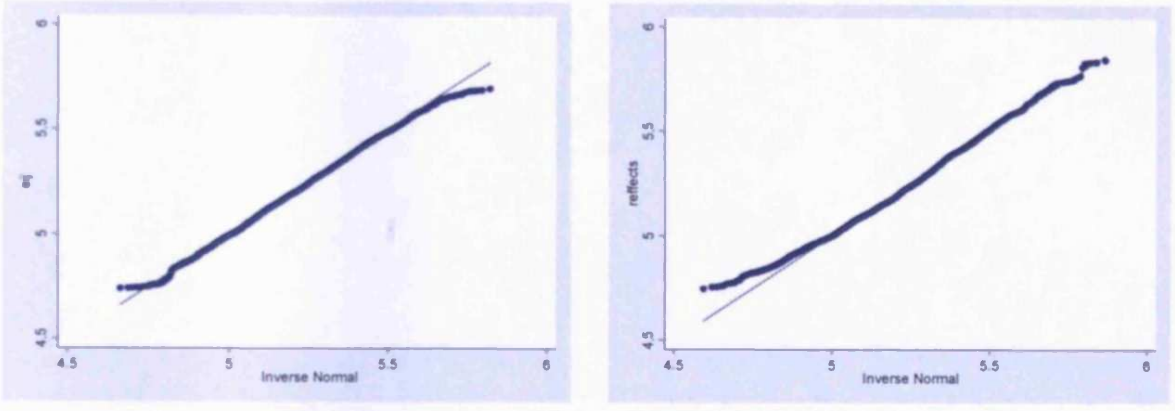
Therefore the final model could be written as:

$$lncost_{ij} = \left[\begin{array}{l} \left(\begin{array}{l} 5.087 - 0.213(nat_i) + 0.002(time_{ij}) + 0.156(initreg1_{ij}) + \\ 0.167(initreg2_{ij}) - 0.009(age_{ij}) + 0.086(cd4cat1_{ij}) + \\ 0.115(cd4cat2_{ij}) + 0.148(vlcat1_{ij}) + 0.147(hivstage2_{ij}) \end{array} \right) \\ + \left(\zeta_{1i}(time_{ij}) + \zeta_{0i} + e_{ij} \right) \end{array} \right]$$

where

lncost	Natural log of outpatient care monthly cost
time	Time in monthly unit
age	Age of patient
cd4cat1	Categorization of CD4+ count <250 cells/mm^3 at time j
cd4cat2	Categorization of CD4+ count 250 – 500 cells/mm^3 at time j

vlcat1	Categorization of viral load < 1000 at time j
initreg1	Initial antiretroviral regimen with PHAART
initreg2	Initial antiretroviral regimen with NHAART
hivstage2	Stage of HIV infection (AIDS) at time j
nat	Nationality (British) on recruitment



a) Level One b) Level Two

Figure 3.6 Normal probability plot for the raw residuals at level one, e_{ij} and level two, *reffects*

Examining final model tenability

The structural specification of the model assumed linear functional form between logarithm of costs and the predictors while its stochastic specification assumed that the distribution error at level one and two was normal. As the validity of the model fitting rests on assumption tenability, this assumption was tested using a normal probability plot. The plots for the monthly cost data appear linear for both level one (Figure 3.6a) and two residuals (Figure 3.6b) confirming the linear assumption made for the functional relationship between outcomes and level one and level two predictors. This also indicates that the residuals were normally distributed. It was therefore safe to conclude that the assumption made in the model fitting on the data of HIV patient's were satisfactorily met and the results were valid.

Table 3.9 Results of fitting a taxonomy of multilevel models for change in level one (n=150)

Structural Part

		Parameter	Model A	Model B	Model C1	Model C2	Model C3	Model C4
Fixed Effects	Intercept	γ_{00}	5.258**** (0.034)	5.185**** (0.041)	5.138**** (0.045)	5.095**** (0.048)	4.906**** (0.067)	4.890**** (0.069)
Rate of change, π_{1i}	Intercept	γ_{10}		0.002 (0.001)	0.002 (0.001)	0.002 (0.001)	0.002*** (0.001)	0.002*** (0.001)
Rate of change, π_{2i}	Intercept	γ_{20}			0.1541* (0.081)	0.148* (0.080)	0.160*** (0.082)	0.116 (0.090)
Rate of change, π_{3i}	Intercept	γ_{30}			0.096* (0.053)	0.106** (0.052)	0.173*** (0.057)	0.134* (0.072)
Rate of change, π_{4i}	Intercept	γ_{40}				-0.010** (0.004)	-0.010*** (0.004)	-0.010*** (0.004)
Rate of change, π_{5i}	Intercept	γ_{50}					0.086*** (0.042)	0.086** (0.042)
Rate of change, π_{6i}	Intercept	γ_{60}					0.115*** (0.057)	0.114** (0.057)
Rate of change, π_{7i}	Intercept	γ_{70}					0.149**** (0.039)	0.161**** (0.041)
Rate of change, π_{8i}	Intercept	γ_{80}					0.155*** (0.074)	0.145** (0.074)
Rate of change, π_{9i}	Intercept	γ_{90}						0.065 (0.056)
Rate of change, π_{10i}	Intercept	γ_{100}						0.053 (0.060)

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ; π_1 = time; π_2 = initial PHAART ; π_3 = initial NHAART; π_4 = age; π_5 = CD4 < 250; π_6 =CD4 200 - 500;

π_7 =Viral Load > 1000; π_8 =HIV Symptomatic; π_9 =HIV AIDS; π_{10} =current PHAART

Table 3.9 Results of fitting a taxonomy of multilevel models for change in level one (n=150) (cont)

Stochastic Part

		Parameter	Model A	Model B	Model C1	Model C2	Model C3	Model C4
Variance Components								
Level 1	Within person	σ_e^2	-0.251 (0.011)	-0.271 (0.011)	-0.271 (0.011)	-0.271 (0.011)	-0.273 (0.011)	-0.273 (0.011)
Level Two	In initial status	σ_0^2	-0.969 (0.070)	-5.383 (0.147)	-5.393 (0.149)	-5.414 (0.157)	-5.367 (0.146)	-5.364 (0.145)
	In rate of change	σ_1^2		-0.836 (0.074)	-0.852 (0.076)	-4.385 (0.725)	-0.885 (0.079)	-0.881 (0.079)
	In rate of change	σ_4^2				-0.917 (0.095)		

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change

Level-1 Variable	Level-2 Variable	Parameter	Model D1	Model D1	Model D2	Model D3	Model D4	Model F
Initial status, π_{0i}	Intercept	γ_{00}	5.258**** (0.034)	4.902**** (0.068)	4.908**** (0.068)	4.133**** (0.327)	4.872*** (0.069)	5.087**** (0.106)
	male	γ_{01}	-0.415** (0.194)					
	nat1	γ_{05}						-0.213** (0.096)
	ethn1	γ_{010}				0.790** (0.333)		
	ethn2	γ_{011}				0.936** (0.372)		
	ethn3	γ_{012}				0.230 (0.616)		
Rate of change, π_{1i}	Intercept	γ_{10}	0.002 (0.001)	0.001 (0.002)	0.002* (0.001)	0.005 (0.006)	0.003**** (0.001)	0.002*** (0.001)
	male	γ_{11}	0.000 (0.003)					
	loc1	γ_{12}		0.002 (0.002)				
	rf1	γ_{13}			0.000** (0.002)			
	rf2	γ_{14}			-0.006* (0.003)			
	emp1	γ_{17}					0.000 (0.002)	
	emp2	γ_{18}					0.005 (0.007)	
	emp3	γ_{19}					-0.003 (0.009)	

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ; π_1 = time

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change (cont 1)

Level-1 Variable	Level-2 Variable	Parameter	Model D1	Model D1	Model D2	Model D3	Model D4	Model F
Rate of change, π_{1i}	ethn1	γ_{110}				-0.002 (0.006)		
	ethn2	γ_{111}				-0.002 (0.007)		
	ethn3	γ_{112}				0.005 (0.008)		
Rate of change, π_{2i}	Intercept	γ_{20}	0.206 (0.215)	0.039 (0.137)	-0.281** (0.147)	0.185** (0.090)	0.133 (0.120)	0.156*** (0.081)
	male	γ_{21}	-0.047 (0.232)					
	loc1	γ_{22}		0.174 (0.169)				
	rf1	γ_{23}			-0.179 (0.160)			
	rf2	γ_{24}			0.160 (0.314)			
	emp1	γ_{27}					0.010 (0.165)	
	emp2	γ_{28}					0.396 (0.444)	
	emp3	γ_{29}					-	
	ethn1	γ_{210}				-0.001 (0.002)		
	ethn2	γ_{211}				-		
	ethn3	γ_{212}				-		

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ; π_1 = time; π_2 = initial PHAART

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change (cont 2)

Level-1 Variable	Level-2 Variable	Parameter	Model D1	Model D1	Model D2	Model D3	Model D4	Model F
Rate of change, π_{3i}	Intercept	γ_{30}	0.006 (0.141)	0.065 (0.098)	0.224*** (0.087)	0.211** (0.074)	0.255**** (0.066)	0.167*** (0.057)
	male	γ_{31}	0.200 (0.154)					
	loc1	γ_{32}		0.156 (0.115)				
	rf1	γ_{33}			-0.073 (0.114)			
	rf2	γ_{34}			-0.054 (0.233)			
	emp1	γ_{37}					-0.005*** (0.002)	
	emp2	γ_{38}					0.002 (0.008)	
	emp3	γ_{39}					0.007 (0.171)	
	ethn1	γ_{310}				-0.003* (0.002)		
	ethn2	γ_{311}				-0.003 (0.006)		
	ethn3	γ_{312}				0.007 (0.007)		
Rate of change, π_{4i}	Intercept	γ_{40}	-0.024* (0.012)	-0.007 (0.007)	-0.015*** (0.006)	-0.064*** (0.023)	-0.009 (0.006)	-0.009** (0.004)
	gender2	γ_{41}	0.012 (0.013)					

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ; π_3 = initial NHAART; π_4 = age

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change (cont 3)

Level-1 Variable	Level-2 Variable	Parameter	Model D1	Model D1	Model D2	Model D3	Model D4	Model F
Rate of change, π_{4i}	loc1	γ_{42}		-0.004 (0.008)				
	rf1	γ_{43}			0.006 (0.810)			
	rf2	γ_{44}			0.029 (0.019)			
	emp1	γ_{47}					-0.001 (0.008)	
	emp2	γ_{48}					-0.003 (0.026)	
	emp3	γ_{49}					-0.063* (0.034)	
	ethn1	γ_{410}				0.060*** (0.023)		
	ethn2	γ_{411}				0.035 (0.025)		
	ethn3	γ_{412}				0.004 (0.040)		
Rate of change, π_{5i}	Intercept	γ_{50}	-0.200* (0.119)	0.143** (0.067)	0.012 (0.062)	0.022 (0.242)	-0.069 (0.052)	0.086** (0.042)
	gender2	γ_{51}	0.319** (0.127)					
	loc1	γ_{52}		-0.079 (0.079)				
	rf1	γ_{53}			0.105 (0.075)			
	rf2	γ_{54}			0.247 (0.212)			

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ;π_4 = age; π_5 = $CD4 < 250$

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change (cont 4)

Level-1 Variable	Level-2 Variable	Parameter	Model D1	Model D1	Model D2	Model D3	Model D4	Model F
Rate of change, π_{5i}	emp1	γ_{57}					0.058 (0.075)	
	emp2	γ_{58}					-0.109 (0.324)	
	emp3	γ_{59}					-0.213 (0.282)	
	ethn1	γ_{510}				0.058 (0.247)		
	ethn2	γ_{511}				0.058 (0.279)		
	ethn3	γ_{512}				-0.406 (0.401)		
Rate of change, π_{6i}	Intercept	γ_{60}	-0.190 (0.142)	0.163* (0.097)	0.045 (0.091)	0.432 (0.435)	0.112 (0.069)	0.115** (0.056)
	male	γ_{61}	0.342** (0.154)					
	loc1	γ_{62}		-0.065 (0.106)				
	rf1	γ_{63}			0.247 (0.212)			
	rf2	γ_{64}			0.270 (0.266)			
	emp1	γ_{67}					0.086 (0.103)	
	emp2	γ_{68}					-0.509 (0.445)	
	emp3	γ_{69}					-0.621 (0.570)	

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ; π_5 = CD4 < 250; π_6 =CD4 250 - 500

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change (cont 5)

Level-1 Variable	Level-2 Variable	Parameter	Model D1	Model D1	Model D2	Model D3	Model D4	Model F
Rate of change, π_{6i}	ethn1	γ_{610}				-0.331 (0.439)		
	ethn2	γ_{611}				-0.337 (0.507)		
	ethn3	γ_{612}				-0.670 (0.590)		
Rate of change, π_{7i}	Intercept	γ_{70}	0.068 (0.107)	0.042 (0.070)	0.143** (0.067)	-0.049 (0.255)	0.100** (0.048)	0.148**** (0.039)
	male	γ_{71}	0.091 (0.112)					
	loc1	γ_{72}		0.142 (0.076)				
	rf1	γ_{73}			-0.001 (0.074)			
	rf2	γ_{74}			0.215 (0.178)			
	emp1	γ_{77}					0.112 (0.075)	
	emp2	γ_{78}					0.200 (0.285)	
	emp3	γ_{79}					-0.150 (0.365)	
	ethn1	γ_{710}				0.193 (0.259)		
	ethn2	γ_{711}				0.177 (0.294)		
	ethn3	γ_{712}				0.173 (0.332)		

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ;π_6 =CD4 200 - 500;π_7 =Viral Load > 1000

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change (cont 6)

Level-1 Variable	Level-2 Variable	Parameter	Model D1	Model D1	Model D2	Model D3	Model D4	Model F
Rate of change, π_{8i}	Intercept	γ_{80}	0.233 (0.257)	0.310*** (0.107)	0.219** (0.112)	1.768**** (0.437)	0.173* (0.103)	0.147*** (0.073)
	male	γ_{81}	-0.087 (0.269)					
	loc1	γ_{82}		-0.239* (0.141)				
	rf1	γ_{83}			-0.062 (0.134)			
	rf2	γ_{84}			-0.237 (0.242)			
	emp1	γ_{87}					-0.026 (0.139)	
	emp2	γ_{88}					0.057 (0.334)	
	emp3	γ_{89}					-0.084 (0.491)	
	ethn1	γ_{810}				-1.660**** (0.443)		
	ethn2	γ_{811}				-1.705**** (0.496)		
	ethn3	γ_{812}						

p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ;π_8 = AIDS

Table 3.10 Results of fitting level-2 variable into taxonomy of multilevel models for change (cont 7)

Stochastic part

Variance in Level 1	Within person	σ_{ε}^2	-0.273 (0.011)	-0.273 (0.011)	-0.273 (0.011)	-0.276 (0.011)	-0.274 (0.113)	-0.273 (0.011)
Variance in Level Two	In initial status	σ_0^2	-5.365 (0.147)	-5.345 (0.145)	-5.338 (0.146)	-5.311 (0.148)	-5.382 (0.151)	-5.349 (0.145)
	In rate of change	σ_1^2	-0.889 (0.079)	-0.885 (0.079)	-0.874 (0.080)	-0.919 (0.080)	-0.901 (0.082)	-0.898 (0.079)
	Covariance	σ_{01}						

DISCUSSION

In this study, the mean monthly cost of outpatient care for a patient was estimated to be £237.59 (±152.32). This estimate was similar to the one reported by (Flori and le Vaillant, 2004)) of £221.10. However, this was much higher than estimated by two other US studies that reported a monthly cost of £48.87 and £89.03 (Bozzette et al., 2001, Simpson et al., 2004). It is very difficult to explore the reason for this difference due to lack of information on resource definitions. However, one of the reasons for the difference might be due to the heterogeneity of study design. A study by Bozzette (2001) was based on patient interviews regarding resource utilization whereas this study relied on the clinic's medical records. This difference could also be due to more rigorous clinic routine monitoring for patients accounted in the present study including resistance test even for newly diagnosed treatment naïve patient which was outlined in the recent British HIV Association's guidelines (Gazzard, 2005). Other factors that could explain the variation were the differences in local health system HIV management.

The monthly costs of patient care were made up largely by clinic consultation and laboratory costs (Figure 3.7). While the imaging and procedure costs were almost constant, the clinic consultation cost decreased over time. The laboratory cost however showed an increasing trend over time. The pattern seen could be a manifestation of patients' HIV progression to a more severe HIV stage whereby more resources were used for monitoring purposes. As was later confirmed in the multilevel analysis of change in monthly cost, patients in AIDS stage had a 14.7% higher monthly cost than patients with no AIDS. ($p<0.05$). This echoed results reported from a previous study (Yazdanpanah et al., 2002).

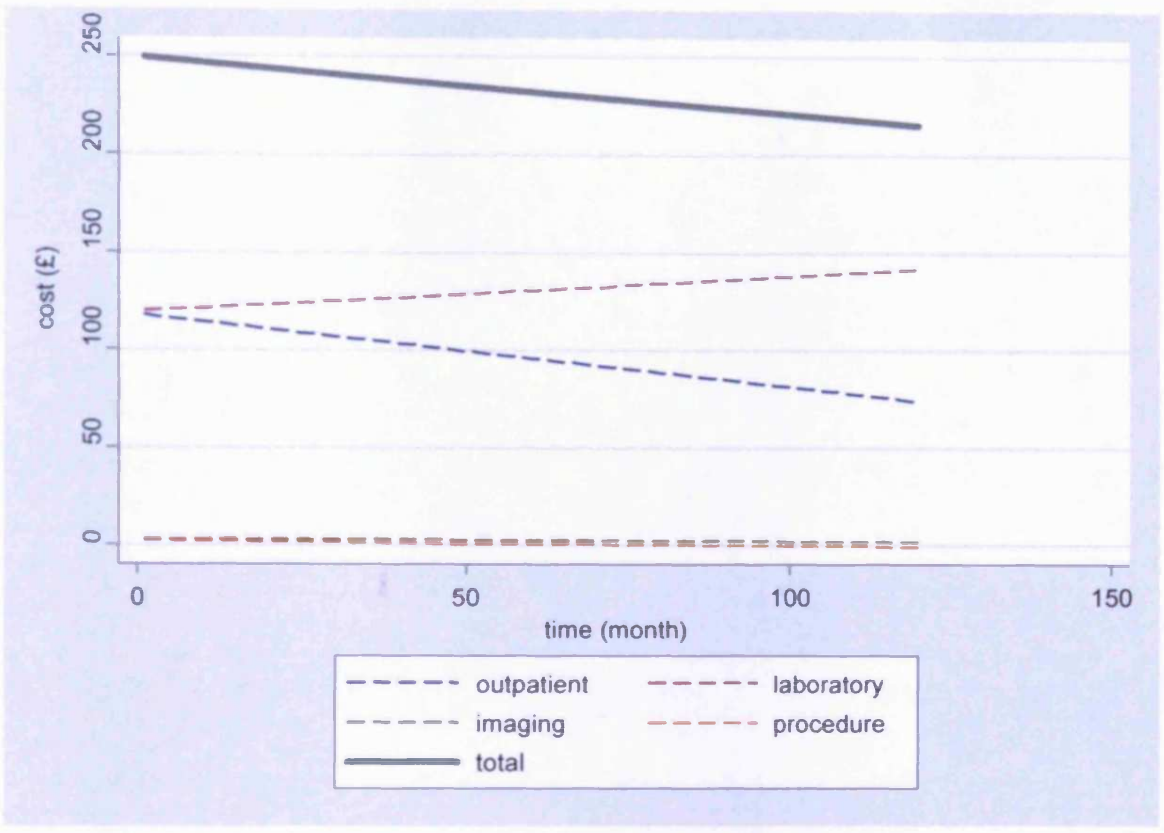


Figure 3.7 OLS fit of outpatient care component cost

In the multilevel analysis of change in monthly cost, it was found that the monthly cost for average patients with no antiretroviral regimen or not on HAART regimens, more than 500 cells/mm^3 CD4 count, more than 1000 copies/ml viral load count, no AIDS and non British was £192.10. This cost increased by 0.2% every month after controlling for these predictors.

It was also found that patients' demographic attribute did not affect the monthly cost except for nationality. British nationals were estimated to have 21.3% less costs compared with non British nationals after adjusting for initial HAART regimen, CD4 count, viral load, stage of HIV infection, and time. This suggests that provision of HIV care in the trust should take into account the distribution of migrant seen in the clinic.

One important feature of the multilevel model is the ability to include a time varying predictor in the model. As a patient could change clinical attributes (CD4, VL, HIV stage) over time due to disease progression and treatment, it is important to incorporate this change in estimating and exploring monthly costs.

As expected, time varying predictor, CD4 count, the amount of HIV virus in plasma and stage of HIV infections had significant effect on the rate of change in monthly costs. Patients with the lowest CD4 stratum (<200) which indicates a severe deficiency of the patients immune system had 8.6% higher monthly cost than patients with a CD4 count of >500. Surprisingly however, patients in the middle CD4 stratum (200 – 500) had 2.9% higher cost than patient with CD4 <200. This contradicts previous belief's that patients with lower immunity systems incur higher costs. This could possibly caused by patients receiving more intensive outpatient care in this stratum. It is difficult to explain the difference however as this study excluded acute care costs and cost had incurred in general practitioner's clinic.

The main focus in this study was to explore the effect of initial regimen on monthly cost. It was found that the initial regimen was a significant predictor of the rate of change in monthly cost. Patients receiving NHAART had 1.1% percent average difference over time of monthly cost more than patients receiving PHAART as the initial treatment. This could be because of the cross resistance of patients with NHAART, whereby patients need to be more intensively monitored or perhaps due to the toxicity of the NHAART regimen itself. The causality of this trend could not be explored in this study but a future study could certainly explore this. On the other hand, current regimens did not have any effect on the change. This finding underlined the importance of initial regimens selection for HIV patients.

SUMMARY

- The unadjusted mean monthly cost of outpatient care for a patient was estimated to be £237.59 (±152.32).
- The monthly cost of patient care was made up largely by the clinic consultation and laboratory cost though clinic consultation cost decreased over time.
- The mean monthly cost of outpatient care for a patient, after adjusting for nationality, time, initial regimen, age, CD4 count, amount of HIV virus in plasma, and stage of HIV infection was estimated to be £192.10.
- Initial regimen was a significant predictor of rate of change in monthly cost with patients that received initial NHAART regimens having 1.1% percent average difference over time of monthly cost more than patients receiving PHAART as the initial treatment.
- Other factors that influence monthly cost were nationality, CD4+ count, viral load, and HIV stage.

Chapter 4

Study II: Quality of Life of Patients with HIV

INTRODUCTION

Health related quality of life (HRQoL) of patients with HIV has been demonstrated to be lower than the general population and patients in AIDS stage of HIV were reported to have lower HRQoL than other patients with chronic disease e.g. cancer (Miners et al., 2001a, Hays et al., 2000). As such, HRQoL was recognized as one of the most important outcomes in treating patients with HIV (Forum for Collaborative HIV Research, 1999a).

Highly Active Antiretroviral Treatment (HAART) has increased life expectancy for HIV patients. Unfortunately it came at the cost of toxicity from the combination of antiretroviral agent in the regimens. The type and severity of toxicity however differed from one agent to another and could generally be attributed to their pharmacological class.

Patients receiving protease inhibitor (PI) class drugs are more prone to severe metabolic and gastrointestinal adverse effects which often lead to early treatment discontinuation (John et al., 2001, Moyle and Carr, 2002). Although non nucleoside reverse transcriptase inhibitor (NNRTI) drugs didn't exhibit this effect, patient's receiving them had adverse effects associated with long term neurology and psychiatry (Treisman and Kaplin, 2002). Unfortunately, the current body of knowledge has yet to ascertain the effect of the different HAART regimen combinations on preference based HRQoL.

The objective of this study therefore was to explore the effect of different initial HAART regimens on patients' health related quality of life. The secondary objective in this study was investigating clinical and demographic factors that could influence HIV patients' health related quality of life (HRQoL).

METHODS

Study Design

This study was performed as a longitudinal observational study. All patients' attending outpatient HIV clinic that had consented to the study between November 2004 and December 2005 were included in this study. Patients with severe psychiatric problems were excluded. Study patients were required to complete a Health Utility Index 3 (HUI3) questionnaire on consent (baseline) and two other questionnaires by post after three and six months.

Sample Size Estimation

The number of subjects needed per group, *m* was determined as follows (Diggle et al., 1996):

$$m = \frac{2(z_{\alpha} + z_{Q})^2 \sigma^2 (1-\rho)}{n s_x^2 d^2}$$

Where

d	Smallest meaningful difference of interest to be detected
Q	Obtained by subtracting P, statistical power to reject the null hypothesis when it is incorrect from 1 (i.e. 1 – P).
σ	Measurement variation.
ρ.	The correlation among the repeated observations.
α,	The type I error rate.
s_x^2	Within-subject variance of explanatory variable.
x_j	Duration between the first and the *j*th visit.

For the 80% (P) power of detecting quality of life difference, d between monthly times of six months (n), at the level of 5% significance (α), the number needed per group according to correlation, ρ and measurement variation, σ^2 was as in Table 4.1. The smallest meaningful difference, d was assumed to be 0.03 unit (Hays and Woolley, 2000).

Table 4.1 Sample size needed per group for selected values of correlation, ρ and smallest meaningful difference in standard deviation unit, Δ

	σ^2		
ρ	0.08	0.1	0.2
0.2	49.38	61.73	123.46
0.5	30.86	38.58	77.16

Therefore, the number of subjects per group needed to be at least 30 for the intended study duration. The sample size however needs to be larger with higher measurement variation among the repeated observations.

Ethics Approval

Ethics approval was obtained from the South East Wales Research Ethics Committees on the 24th September 2004 (see Appendix I).

Data Collection

The first step for patient recruitment is patient identification. The HIV patient in Cardiff Royal Infirmary was easier to identify than in University Hospital of Wales (UHW) as the Infectious Disease Clinic in UHW was attended by non HIV patients as well. For privacy and sensitivity reasons, researcher was not allowed to identify the patient by name and was discouraged from approach patient in the general

waiting room. For these reasons, the identification step relies heavily on cooperation from clinic staff members.

Patients identified were approached upon staff introduction and the nature of the study was explained verbally and a printed study information sheet (Appendix II) was given to the patient. Upon verbal and written consent (Appendix III), patients were then required to complete a Health Utility Index 3 (HUI3) questionnaire (baseline, T1) and complete two more questionnaires by post after three (T2) and six months (T3). If required, patient completion of HUI3 questionnaire was assisted by a researcher through reading aloud or recording their responses on the questionnaire. Other variables recorded for analysis include: risk factor; employment; status; gender; nationality; antiretroviral treatment; viral load; CD4+ count; and HIV stage.

Health Related Quality of Life Instrument

HUI3 is a health related quality of life (HRQoL) questionnaire consisting of a set of health status classifications and an accompanying set of utility weight (Feeny et al., 2002, Horsman et al., 2003). The classification system has eight dimensions which are: vision; hearing; ambulation; dexterity; speech; emotion; cognitive; and pain. Each dimension has three to five levels, potentially defining a total of 972,000 states. The HRQoL scale is defined for the interval 0.36 to 1.00. 0 is dead and 1 is perfect health. Negative scores represent states considered worse than dead.

The completed HUI3 questionnaire was scored as multi-attribute utility function as in Table 4.2.

Table 4.2 HUI3 multi-attribute utility function on dead-healthy scale

Vision		Hearing		Speech		Ambulation		Dexterity		Emotion		Cognition		Pain	
x_1	b_1	x_2	b_2	x_3	b_3	x_4	b_4	x_5	b_5	x_6	b_6	x_7	b_7	x_8	b_8
1	1.00	1	1.00	1	1.00	1	1.00	1	1.00	1	1.00	1	1.00	1	1.00
2	0.98	2	0.95	2	0.94	2	0.93	2	0.95	2	0.95	2	0.92	2	0.96
3	0.89	3	0.89	3	0.89	3	0.86	3	0.88	3	0.85	3	0.95	3	0.90
4	0.84	4	0.80	4	0.81	4	0.73	4	0.76	4	0.64	4	0.83	4	0.77
5	0.75	5	0.74	5	0.68	5	0.65	5	0.65	5	0.46	5	0.60	5	0.55
6	0.61	6	0.61			6	0.58	6	0.56			6	0.42		

Where x_n is the attribute level and b_n is the attribute utility score

The formula to calculate global HRQoL score for a patient is given as

$$u^* = 1.371 (b1 * b2 * b3 * b4 * b5 * b6 * b7 * b8) - 0.371$$

where u^* is the HRQoL of a chronic health state.

The construct validity of HUI3 had well been established in previous studies (Feeny et al., 2002, Furlong et al., 2001). Its validity and reliability among HIV population had also been previously ascertained (McCabe et al., 2005, Bayoumi and Redelmeier, 1999).

Missing Data

Missing data was imputed using multiple imputations in *ice* module of STATA. Details of this approach were given in 'Study Plan, Data Processing and Analysis' section in Chapter 2. The imputation model for the missing values was specified according to the type of variables. Ordinal logistic regression was used in the prediction model for missing data in categories of HIV stage as the categories are ordered by their severity. This was specified in the *cmd* option in the *ice* module.

Other unordered categorical variables including employment, risk factor and nationality were predicted by multinomial logistic regression model while missing score for each component of HUI3 was imputed using linear regression. Full syntax implementation of the imputation in STATA was outlined in Appendix VIII.

Data Processing and Analysis

As in study I, the dataset was first transformed in order to improve statistical analysis and interpretability. This was done in the present study by the following:

- Quality of life score was transformed to cubic as it was found to be non linear with time in initial exploratory analysis.
- Age was centred on mean of 40 years old for better interpretation of results (Singer and Willett, 2003).
- Dummy variables, with only values of zero or one, were created for categorical variables with more than two levels.

Table 4.3 gives full description of the transformed variables.

Cross Sectional Analysis

Descriptive demographic, clinical and quality of life scores were tabulated and analyzed at baseline (T1), second questionnaire completion (T2) and third questionnaire completion (T3) for background of the study sample. This was followed by fitting the explanatory variables (see Table 4.3) with a multivariate regression model at each cross section time.

Table 4.3 Variables codebook collected and included in the analysis

	Description	Variable Name	Note
Y1	Quality of life score	qolscore^3	Cubic of qolscore
X1	Time difference between questionnaire completion	time	In monthly unit
X2	Antiretroviral regimen at time *j*	curreg1	1=phaart;0=other
X3		curreg2	1=nhaart;0=other
X4		curreg3	1=non haart, no ARV;0=other
X5	Stage of HIV infection at time *j*	hivstage1	1=asymptomatic;0=other
X6		hivstage2	1=symptomatic, AIDS;0=other
X7	Categorization of CD4+ count at time *j*	cd4cat1	1=<200;0=other
X8		cd4cat2	1=201-500;0=other
X9		cd4cat3	1=>500;0=other
X10	Categorization of viral load at time *j*	vlcat1	1=<1000;0=other
X11		vlcat2	1=>1000;0=other
X12	Initial antiretroviral regimen	initreg1	1=phaart;0=other
X13		initreg2	1=nhaart;0=other
X14		initreg3	1= non haart, no ARV;0=other
X15	Factors associated with increased risk for HIV transmission	riskfactor1	1=homosexual; 0=other
X16		riskfactor2	1=heterosexual;0=other
X17		riskfactor3	1=ivdu;0=other
X18		riskfactor4	1=transfusion;0=other
X19	Nationality	nat	1=british;0=other
X20	Ethnicity	ethn1	1=white;0=other
X21		ethn2	1=black;0=other
X22		ethn3	1=asian;0=other
X23		ethn4	1=mixed;0=other
X24	Employment status on recruitment	emp	1=employed;0=other
X25	Primary outpatient care clinic	loc	1=cri,2=uhw
X26	Gender	female	1=female,0=male
X27	Age	age	Age - grand mean (40)

Longitudinal Data Analysis

Preliminary analysis of data suggested that the quality of life of patients deteriorate from baseline after three months (Salek et al., 2006). Therefore, multilevel models (MLM) of changes were used to assess:

- *Within individual change*: How does each patient's quality of life change over time?

- *Interindividual differences in change*: What predict differences among patients in their changes?

Data were first longitudinally explored to identify important features in the dataset and prepare for subsequent model-based analysis. The first twelve patients' empirical quality of life trajectory was graphically summarized using non parametric lowess smoothing to assess within individual change. The quality of life scores were later fitted linearly according to their demographic categories to assess change across people.

Based on the notion that multilevel model is a nested structure with the occasions of measurement defining level one and the individuals defining level two, we could specified the multilevel model as the following:

i) Level One

To see whether the quality of life differs systematically with time for each patient, a Simple Linear Model for Individual Change at level one was specified as follows:

$$qolscore_{ij}^{3} = \pi_{0i} + \pi_{1i}(time_{ij}) + e_{ij}$$

In the multilevel model of change, time varying (TV) variable was modelled in level one. These included time in month from baseline, age, CD4+ count, viral load, current treatment regimen, and HIV clinical stage. This could be written in linear form as the following:

Table 4.4 Taxonomy of multilevel model of change for quality of life score

MODEL	LEVEL	SPECIFICATION
A: Unconditional Means Model	Level One; $qolscore^3_{ij}$ =	$\pi_{0i} + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{00} + \zeta_{0i}$
	Composite; $qolscore^3_{ij}$ =	$\gamma_{00} + \zeta_{0i} + e_{ij}$
B: Unconditional Growth Model	Level One; $qolscore^3_{ij}$ =	$\pi_{0i} + \pi_{1i}(time_{ij}) + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{00} + \zeta_{0i}$; $\pi_{1i} = \gamma_{10}$
	Composite; $qolscore^3_{ij}$ =	$\gamma_{00} + \gamma_{10}(time_{ij}) + \zeta_{0i} + e_{ij}$
C3: Adding the main effect of time varying predictors. (HIV Stage)	Level One; $qolscore^3_{ij}$ =	$\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(hivstage2_{ij}) + e_{ij}$
	Level Two	$\pi_{0i} = \gamma_{01} + \zeta_{0i}$; $\pi_{1i} = \gamma_{10}$; $\pi_{2i} = \gamma_{20}$
	Composite	$\left(\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(hivstage2_{ij})\right) + \left(\zeta_{0i} + e_{ij}\right)$

qolscore^3=cubic transformation of quality of life score; time= time difference between questionnaire completion in monthly unit; hivstage2=HIV stage as defined by CDC 1993; emp=employment status; initreg=initial treatment regimen.

Table 4.4 Taxonomy of multilevel model of change for quality of life score (cont. 1).

MODEL	LEVEL	SPECIFICATION
D1: C3 & inclusion of level two submodel. (employment)	Level One; $qolscore^3 =$	$\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(hivstage2_{ij}) + e_{ij}$
	Level Two	$\pi_{0i} = (\gamma_{00} + \gamma_{01}emp_i + \zeta_{0i})\,;\, \pi_{1i} = \gamma_{10} + \gamma_{11}emp_i$
	Composite $qolscore^3_{ij} =$	$(\gamma_{00} + \gamma_{01}emp_i + \gamma_{10}(time_{ij}) + \gamma_{20}(hivstage2_{ij}) + \gamma_{11}time_{ij}(emp_i)) + (\zeta_{0i} + e_{ij})$
D2: D1 & inclusion of level two submodel. (initial regimen)	Level One; $qolscore^3_{ij} =$	$(\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(hivstage2_{ij}) + e_{ij})$
	Level Two	$\pi_{0i} = (\gamma_{00} + \gamma_{01}emp_i + \gamma_{02}initreg1_i + \gamma_{03}initreg2_i + \zeta_{0i})\,;\, \pi_{1i} = \gamma_{10} + \gamma_{11}emp_i\,;\, \pi_{2i} = \gamma_{20}$
	Composite $qolscore^3_{ij} =$	$\begin{pmatrix} \gamma_{00} + \gamma_{01}emp_i + \gamma_{02}initreg1 + \gamma_{03}initreg2 + \gamma_{10}(time_{ij}) + \gamma_{11}time_{ij}(emp_i) + \\ \gamma_{20}(hivstage2_{ij}) \end{pmatrix} + (\zeta_{0i} + e_{ij})$

qolscore^3=cubic transformation of quality of life score; time= time difference between questionnaire completion in monthly unit; hivstage2=HIV stage as defined by Centre for Disease Control and Prevention 1993; emp=employment status.

Table 4.4 Taxonomy of multilevel model of change for quality of life score (cont. 2).

MODEL	LEVEL	SPECIFICATION
D3: D2 without cross level interaction *emp* with *tindexm*	Level One: $qolscore^3_{ij}$ =	$\left(\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(hivstage2_{ij}) + e_{ij}\right)$
	Level Two	$\pi_{0i} = \left(\gamma_{00} + \gamma_{01}emp_i + \gamma_{02}initreg1_i + \gamma_{03}initreg2_i + \zeta_{0i}\right)$; $\pi_{1i} = \gamma_{10}; \pi_{2i} = \gamma_{20}$
	Composite $qolscore^3_{ij}$ =	$\left(\gamma_{00} + \gamma_{01}emp_i + \gamma_{02}initreg1_i + \gamma_{03}initreg2_i + \gamma_{10}(time_{ij}) + \gamma_{20}(hivstage2_{ij}) + \right)$ $+\left(\zeta_{0i} + e_{ij}\right)$

qolscore^3=cubic transformation of quality of life score; time= time difference between questionnaire completion in monthly unit; hivstage2=HIV stage as defined by Centre for Disease Control and Prevention 1993; emp=employment status; initreg=initial treatment regimen.

$$qolscore_{ij}^{3} = \begin{pmatrix} \pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(age_{ij}) + \pi_{3i}(cd4cat1_{ij}) + \pi_{4i}(cd4cat2_{ij}) + \\ \pi_{5i}(vlcat1_{ij}) + \pi_{6i}(curreg1_{ij})\pi_{7i}(curreg2_{ij}) + \pi_{8i}(curreg3_{ij}) + \\ \pi_{9i}(hivstage1_{ij}) + \pi_{10i}(hivstage2_{ij}) + e_{ij} \end{pmatrix}$$

ii) Level Two

Level two models could be used to assess interindividual differences in change. This would include time invariant variables such as gender, location of outpatient care, ethnicity, nationality, initial treatment regimen and employment.

Both level one and level two variables were entered in the model singly by level and retained or removed through single parameter *z* statistics, logic and prior research. Cross level interactions were also analyzed by including interaction in the model. The taxonomy of postulated models with level one, level two and composite specification was summarized in Table 4.4.

RESULTS

A total of 150 patients consented to participate in the study. Four were excluded because of impaired cognition problem. Not all patients completed all three Health Utility Index Mark 3 (HUI3) questionnaires.

Only 43.3% completed all three questionnaires waves, 44.7% completed two waves, while 6% completed only the baseline. The reasons given for follow up refusal include dead, lost interest and annoyance with NHS service. Patients that only partially completed the questionnaire were imputed using multiple imputation technique as previously described. Dataset integrity was detailed again in Figure 4.1.

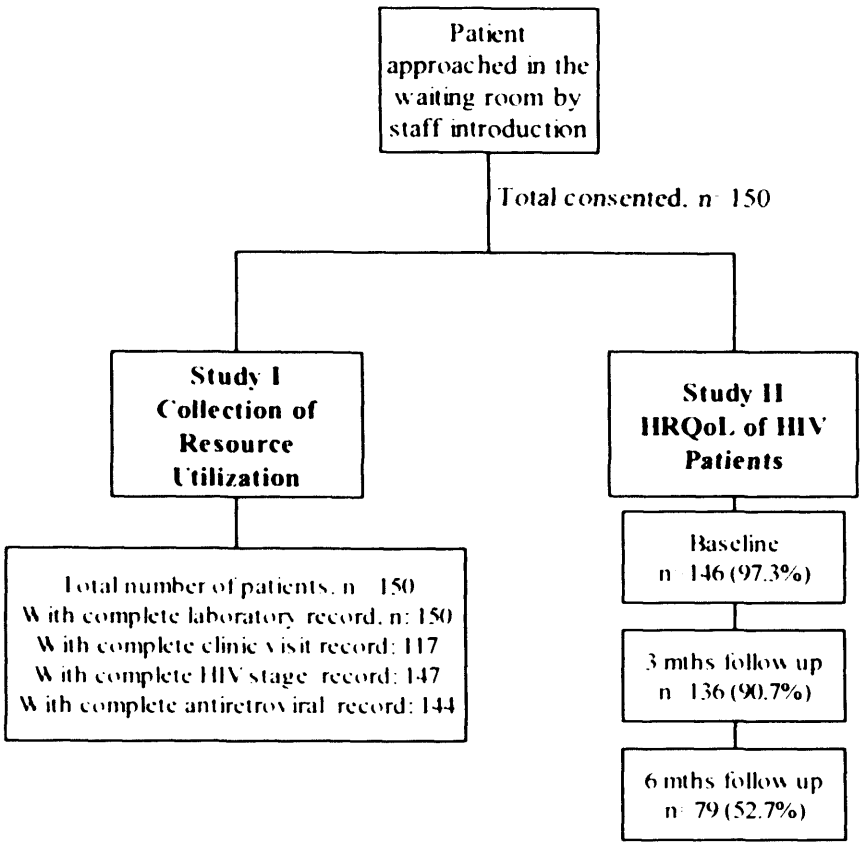


Figure 4.1 Diagram of study design and data completion

Cross Sectional Analysis of Quality of Life

Descriptive Sociodemographic Characteristics

Most of the patients were recruited from HIV Clinic in Cardiff Royal Infirmary (see Table 4.5).

The mean age of patients was 39.7 years (SD=10.0) with 83.0% male. The majority of patients were white (78.9%) and of British nationality (78.2%). Black African constitutes the largest minority ethnicity and nationality. Half of the patients were in employment and more than half of the patients were homosexual while the rest were mostly heterosexual. Other patient risk factors were intravenous drug user (IVDU) and transfusion.

Table 4.5 Sociodemographic characteristics of patients

	T1 (n = 147)		T2 (n = 136)		T3 (n = 79)	
	FREQ	%	FREQ	%	FREQ	%
GENDER						
Female	25	17.01	25	18.38	16	20.25
Male	122	82.99	111	81.62	63	79.75
ETHNICITY						
White	116	78.91	109	80.15	61	77.22
Black	22	14.97	19	13.98	13	16.46
Asian	2	1.36	2	1.47	2	2.53
Mixed	4	2.72	4	2.94	2	2.53
NATIONALITY						
British	115	78.23	108	79.41	60	75.95
African	20	13.61	17	12.50	12	15.19
American	2	1.36	2	1.47	0	0.00
Asian	1	0.68	1	0.74	1	1.27
Other EU	6	4.08	6	4.41	6	7.60
EMPLOYMENT						
Employed	67	48.90	64	47.06	38	48.10
Pensioner	5	3.40	5	3.68	3	3.80
Student	4	2.70	4	2.94	3	3.80
Unemployed	66	44.90	63	46.32	35	44.30
LOCATION						
CRI	99	67.35	92	67.65	44	55.70
UHW	48	32.66	44	32.35	35	44.30
	T1 FREQ	%	T2 FREQ		T3 FREQ	%
RISK FACTOR						
Homosexual	94	63.95	91	66.91	48	60.76
Heterosexual	45	30.61	37	27.21	26	32.91
IVDU	7	4.76	7	5.15	4	5.06
Transfusion	1	0.68	1	0.74	1	1.27

Clinical Parameters

Patients were mostly symptomatic but 19.7% of the patients were already in AIDS stage at baseline (see Table 4.6).

The mean CD4+ count of patients was 450 cells/µl in the range of 20 to 1880 cells/µl. The mean viral load burden of patients was 6.0E+04 copies/ml with maximum of 6.0E+06 copies/ml. Most patients were initially treated with NHAART

treatment regimen. NHAART also were the most frequently regimen used at all three time points of HUI3 questionnaire.

Table 4.6 Clinical parameters

	T1 (n = 147)		T2 (n = 136)		T3 (n = 79)	
	FREQ	%	FREQ	%	FREQ	%
	n=147		n=136		n=79	
CD4						
<200	18	12.24	19	13.97	14	17.72
201-500	83	56.46	90	66.18	50	63.29
>500	46	31.29	27	19.85	15	18.99
VIRAL LOAD						
<1000	109	74.15	111	81.62	66	83.54
>1000	38	25.85	25	18.38	13	16.46
HIV STAGE						
Asymptomatic	29	19.73	29	21.32	18	22.79
Symptomatic	77	52.38	70	51.47	36	45.57
AIDS	41	27.89	37	27.21	25	31.65
INITIAL REGIMEN						
PHAART	29	19.73	25	18.38	14	17.72
NHAART	70	47.62	65	47.79	44	55.70
non HAART	28	19.05	27	19.85	10	12.66
no ARV	20	13.61	19	13.97	11	13.92
CURRENT REGIMEN						
PHAART	35	23.81	32	23.53	17	21.52
NHAART	77	52.38	70	51.47	44	55.70
3NRTI	3	2.04	3	2.21	1	1.27
no ARV	32	21.77	31	22.79	17	21.52

Multivariate Regression Analysis

Sociodemographic and clinical predictors were fitted into linear multivariate regression of quality of life scores at each cross section time i.e. baseline T1, second HUI3 completion (T2), and third HUI3 completion (T3). This resulted in three different fitted models (Table 4.7). At baseline (T1), the mean quality of life score for unemployed and non white patients was 0.6444. Employed patients had 0.0962 units higher of quality of life controlling for white ethnicity. At T2, only employment

was significant predictor of the quality of life score while at T3, AIDS status significantly predicted the cubic form of quality of life score.

Longitudinal Data Analysis

As with any data analysis, this study begins by making displays to expose the

Table 4.7 Determinants of quality of life score at each time cross section

INDEPENDENT VARIABLE						
	T1		T2		T3	
	COEFF	SE	COEFF	SE	COEFF	SE
Employment	0.0962	0.0416	0.1146	0.0506		
White	0.0886	0.0524				
AIDS*					0.0824	0.0579
Constant	0.6444	0.0486	0.6865	0.0345	0.7753	0.0332
Dependent Variable:Quality of Life Score, qolscore * Dependent Variable=Cubic of Quality of Life Score						

patterns relevant to the scientific questions before moving into a more complex statistical analysis. This was done by examining the relationship of the independent and dependent variables with time.

Exploratory Analysis

Cross sectional analysis of quality of life in the previous section resulted in different predicted value at each time point. This finding is emphasized in the following longitudinal exploratory analysis of patients' quality of life.

Examining Empirical Graph Plot for First Twelve Patients

The individual QOL score of twelve patients were plotted against time (Figure 4.2). Most patients had the same intercept area (ID 5, 10, 11, 14). Some patients' quality

of life declined with time (ID 1, 3, 11, 14), some improved (ID 5, 8, 10, 13, 15) and some were stable (ID 4, 9).

This plot illustrated that QoL changed with time but with different rate and initial value. In a scatter plot not shown here, the HRQoL does not seems to be linear with time and therefore need prior transformation. The overall ordinary least square (OLS) fitted value (Figure 4.3) suggested that the general change was towards improving quality of life.

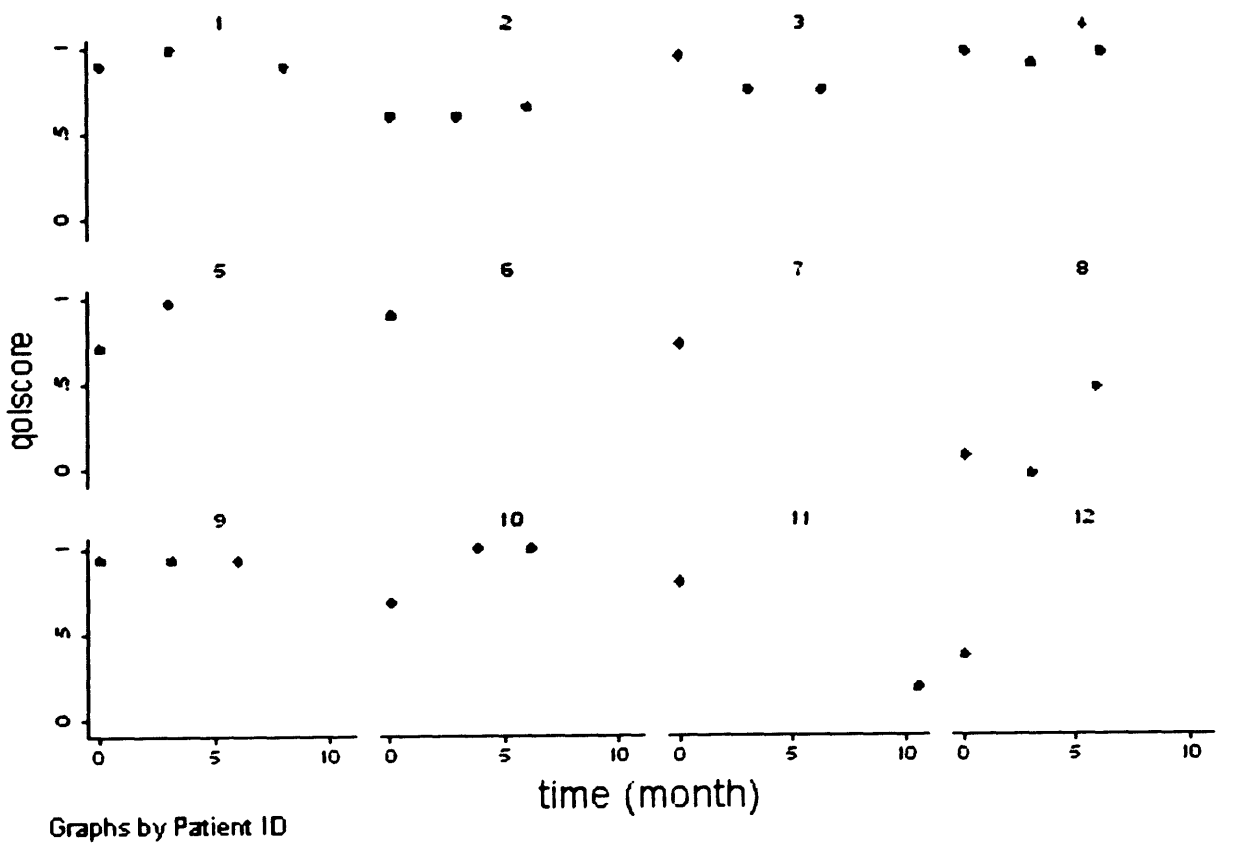


Figure 4.2 Scatter plots of quality of life score for twelve individual patients over time

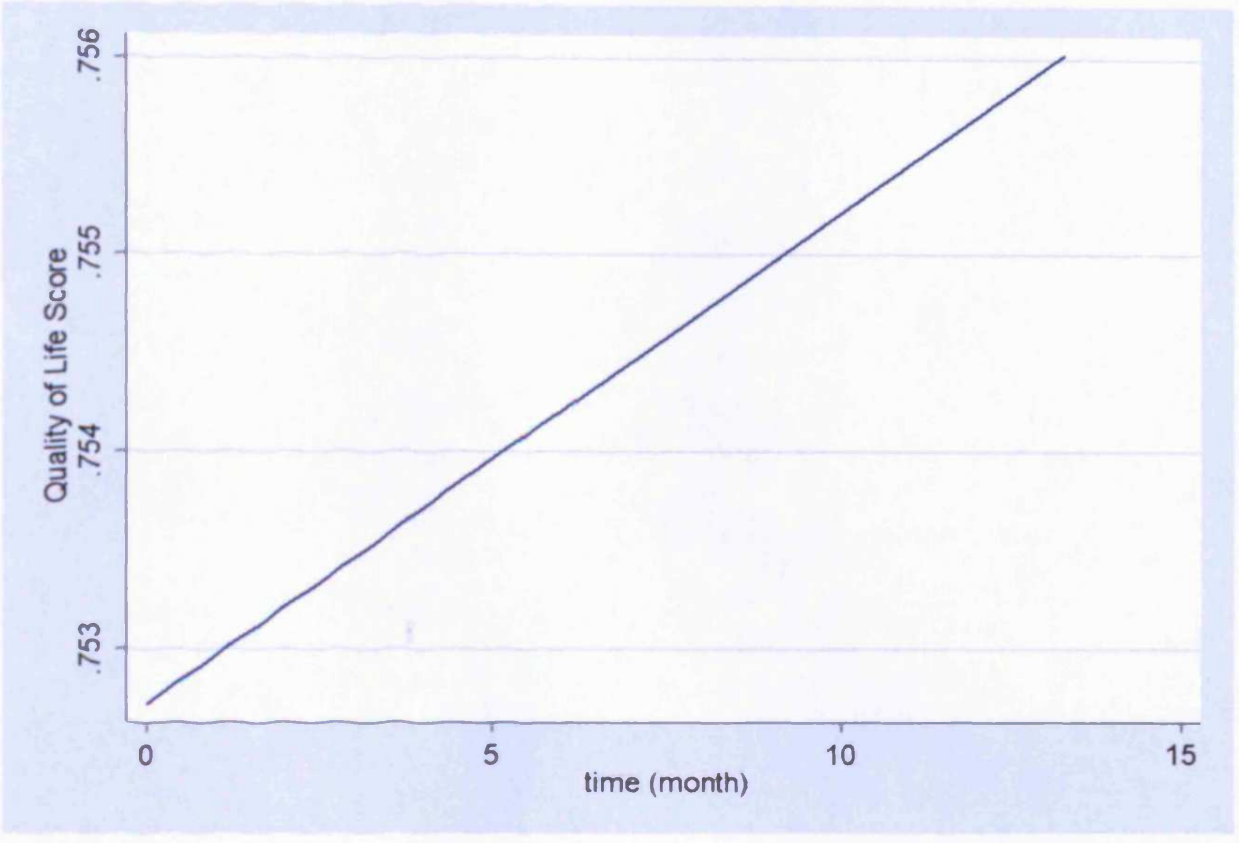


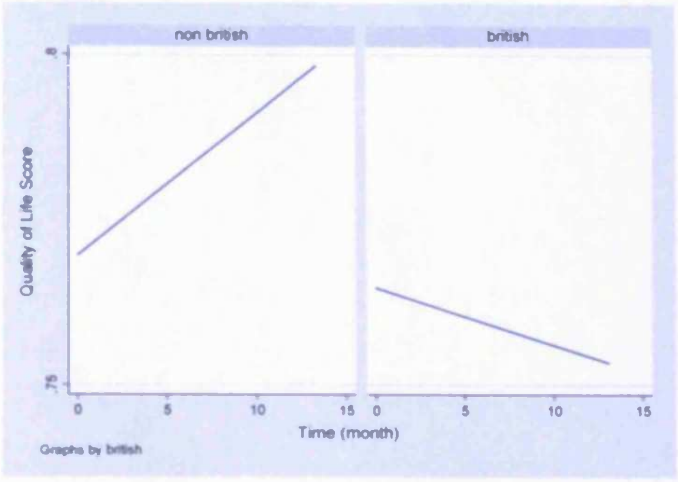
Figure 4.3 Linear fitted values of overall trajectories for all patients in the study over time

Examining factors influencing interindividual differences

The whole 147 cohort was evaluated for the impact of time invariant predictors over time (Figure 4.4). This would help uncover systematic patterns in the individual change trajectories corresponding to interindividual variation in personal characteristics.

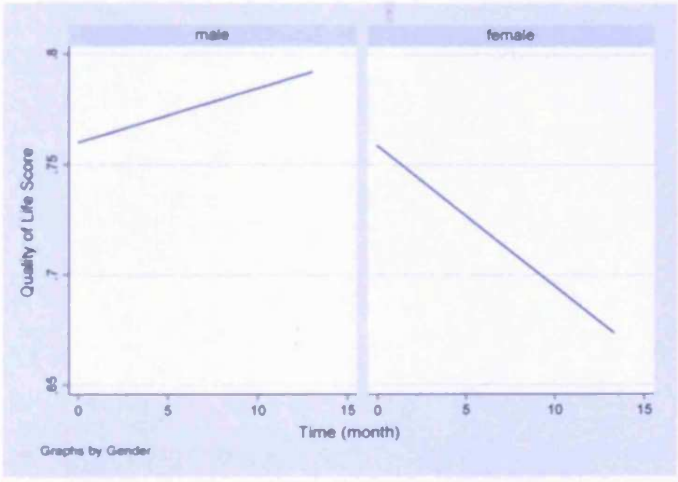
Figure 4.4 Linear prediction of quality of life vs time by time invariant predictors

a) Nationality



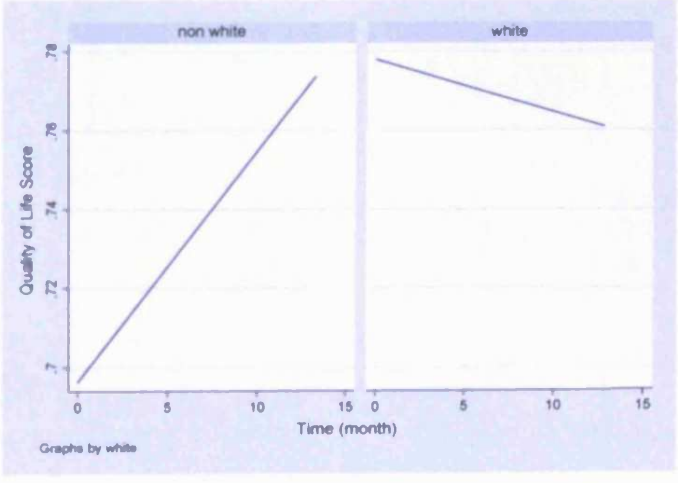
Intercepts were almost at the same point for British and non British patients. But, QoL among British seem to worsen while non British improve.

b) Gender



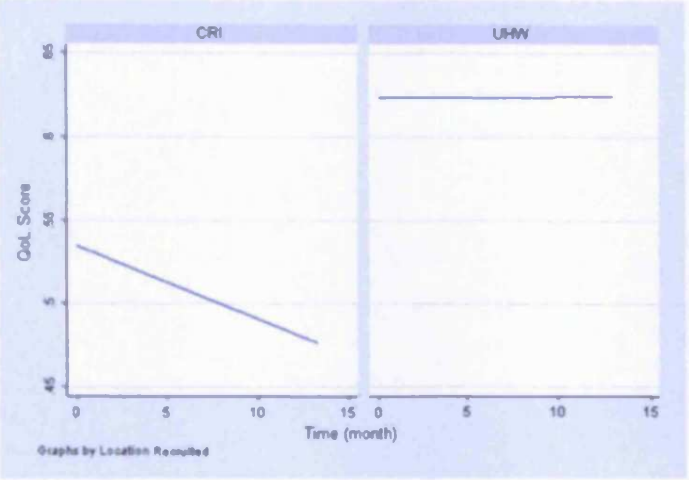
Male and female patients shared the same intercept. Males however improved with time whilst females worsened.

c) Ethnicity



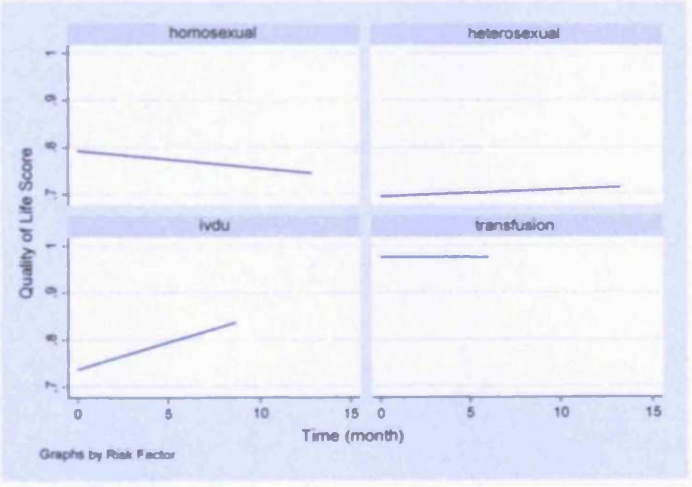
White and non white patients' intercept began at the opposite end of scale. The slope for white patients was negative whereas non white had positive slope.

d) Location



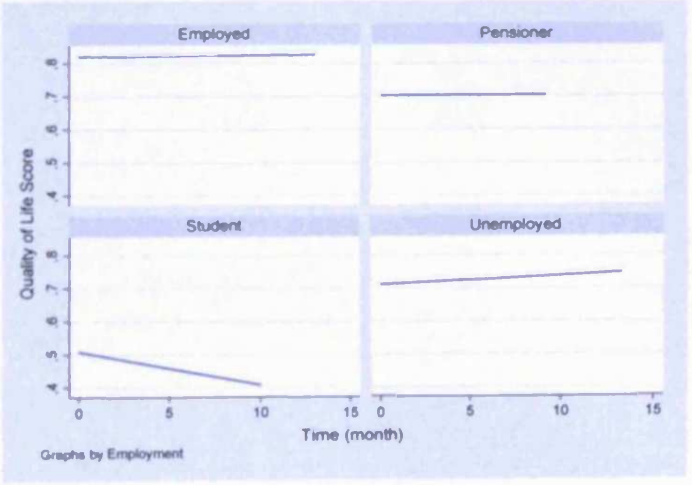
UHW's patients had better baseline score that were almost stable across time. CRI's patients had lower baseline score with negative slope.

e) Risk Factor



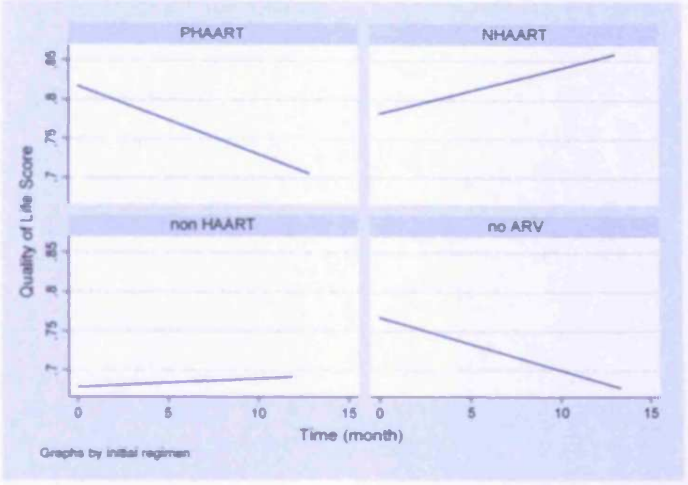
Intercepts also differed among risk factors. The slopes were almost stable for all risk factors except IVDU.

f) Employment



There was difference in intercepts with employed patients had at least 0.1 unit higher than the rest. The slope almost unchanged for all employment status except for student.

g) Initial Treatment Regimen



Intercepts differ between initial treatment regimens with non HAART having the worst baseline score. Slopes also differ with negative slope in PHAART and non ARV.

Fitting Multilevel Model of Change in Quality of Life

Based on the above exploratory analysis, taxonomy of multilevel model was specified as in Table 4.4 (for five selected models). Time and other time varying explanatory variables were specified in level one while time invariant variables were specified in level two. The results of fitting these multilevel models were given in Table 4.8.

Model A: The Unconditional Means Model

$$qolscore_{ij}^{3} = \gamma_{00} + \zeta_{0i} + e_{ij}$$

The estimated grand mean quality of life score across all time and individuals, γ_{00} was,

$= \sqrt[3]{0.5849}$

$= 0.8363$

Rejection of its null hypothesis (p<0.001) confirms that this mean quality of life score for average patients is non zero.

The variance for within individual, σ_e^2 and between person, σ_0^2 were both more than twice its standard deviation indicating that the average quality of life score varies over time and that patients differ from each other in quality of life. The amount of variation between patients regardless of time was given by $\hat{\sigma}_c^2$ and the amount of variation within individuals over time was given by $\hat{\sigma}_0^2$. The intraclass correlation (ICC) that would give the proportion of total variation in Y that lies between patients could be estimated by the following:

$$ICC = \frac{\sigma_0^2}{\sigma_0^2 + \sigma_c^2}$$

$$\therefore ICC = \frac{-1.2961}{-1.2961 - 1.5305} = 0.459$$

An estimated 45.9% of the total variation in chronic care quality of life was attributable to differences among patients. It also means that for each patient, the average correlation between any pair of composite residuals – between T1 and T2, or T2 and T3, or T1 and T3 was 0.459. This was far larger than zero residual autocorrelation assumption that was required in an ordinary least square (OLS) analysis. The role of TIME was evaluated in model B.

Model B: The Unconditional Growth Model

$$qolscore_{ij}^{3} = \gamma_{00} + \gamma_{10}(time_{ij}) + \zeta_{0i} + e_{ij}$$

Where

qolscore	Quality of life score
time	Time difference between questionnaire completion in monthly unit

The null hypothesis estimating that the average true change trajectory for quality of life has a non-zero intercept of 0.5583 was rejected (p<0.001) but could not reject the hypothesis for non-zero slope of 0.0032. This means that there was no linear relationship between cubic of quality of life score and time. However, as the relationship of time with other predictor was also of the study interest, time variable would be preserved in the model.

Model C

$$qolscore_{ij}^{3} = \left(\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(hivstage2_{ij})\right) + \left(\zeta_{0i} + e_{ij}\right)$$

Where

qolscore	Quality of life score
time	Time difference between questionnaire completion in monthly unit
hivstage	Stage of HIV infection at time j

Time varying predictors including CD4+ count, viral load, current regimen, age and stage of HIV infection were fitted in the multilevel model but only symptomatic stage variable (hivstage2) showed promising results (only results for stage of HIV infection were shown).

Table 4.8 Results of fitting taxonomy of multilevel models for change

					Symptomatic	Employment	Initial Reg	Initial Reg
		Parameter	Model A	Model B	Model C	Model D1	Model D2	Model D3
Fixed Effects								
Initial status, π_{0i}	Intercept	γ_{00}	0.5489**** (0.0256)	0.5583**** (0.0280)	0.6027**** (0.0395)	0.5277**** (0.0480)	0.4557**** (0.0568)	0.4745**** (0.0557)
	emp	γ_{01}				0.1710*** (0.0588)	0.1641*** (0.0589)	0.1220** (0.0556)
	initreg1	γ_{02}					0.0845 (0.0798)	0.0860 (0.0800)
	initreg2	γ_{03}					0.1345** (0.0575)	0.1341** (0.0571)
Rate of change, π_{1i}	Intercept	γ_{10}		-0.0032 (0.0039)	-0.0036 (0.0038)	-0.0031 (0.0054)	0.0030 (0.0054)	-0.0035 (0.0039)
	emp	γ_{11}				-0.0140* (0.0082)	-0.0140* (0.0082)	
Rate of change, π_{2i}	Intercept	γ_{20}			-0.0842* (0.0523)	-0.0966* (0.0513)	-0.1072 (0.0512)	-0.1046** (0.0507)
Variance Components								
Level One	Within person	σ_ε^2	-1.5305 (0.0592)	-1.5336 (0.0594)	-1.5343 (0.0600)	-1.5390 (0.0590)	-1.5438 (0.0594)	-1.5371 (0.0820)
Level Two	In initial status	σ_0^2	-1.2961 (0.0781)	-1.2925 (0.0780)	-1.2906 (0.0782)	-1.3170 (0.0810)	-1.3280 (0.0819)	-1.3316 (0.0820)
~p<0.10: * ;p<0.05: **; p<0.01: ***, p<0.001: **** ;π_1 = time;π_2 = HIV symptomatic stage								

The initial cubic quality of life score was estimated to be 0.6027 (P<0.0001) for non symptomatic patients. The estimated differential in initial cubic quality of life score between symptomatic and asymptomatic patients was -0.0842 (P<0.1). The parameter estimate of TIME (*time*), γ_{10} was still not statistically significant.

Model D1

$$qolscore_{ij}^{3} = \left[\begin{pmatrix} \gamma_{00} + \gamma_{01} emp_i + \gamma_{10}(time_{ij}) \\ +\gamma_{20}(hivstage2_{ij}) + \gamma_{11} time_{ij}(emp_i) \end{pmatrix} + \left(\zeta_{0i} + e_{ij}\right) \right]$$

Where

qolscore	Quality of life score
emp	Employment status on recruitment
time	Time difference between questionnaire completion in monthly unit
hivstage	Stage of HIV infection at time j

For unemployed and asymptomatic patients, their initial quality of life score was $\sqrt[3]{0.5277}$ (P<0.0001). Controlling for the effect of HIV stage, the estimated differential in the rate of change in quality of life score was $\sqrt[3]{0.014}$ (P<0.1). Difference in initial status variance, σ_0^2 indicates that inclusion of this variable explained 0.2% of the variation in initial status than model C.

Model D2

$$qolscore_{ij}^{3} = \left[\begin{pmatrix} \gamma_{00} + \gamma_{01} emp_i + \gamma_{02} initreg1_i + \gamma_{03} initreg2_i + \gamma_{10}(time_{ij}) \\ +\gamma_{11} time_{ij}(emp_i) + \gamma_{20}(hivstage2_{ij}) \end{pmatrix} + \left(\zeta_{0i} + e_{ij}\right) \right]$$

Where

qolscore	Quality of life score
emp	Employment status (employed) on recruitment
initreg1	Initial antiretroviral regimen PHAART
initreg2	Initial antiretroviral regimen NHAART
time	Time difference between questionnaire completion in monthly unit
hivstag2e	Stage of HIV infection (symptomatic and AIDS) at time j

Inclusion of another level two predictor i.e. initial regimen of PHAART (initreg1) and NHAART (initreg2) into D1 results in indistinguishable initial quality of life score between symptomatic and asymptomatic patients (-0.1072, ns). Within individual variances, σ_t^2 had also increased 0.5% from D1 indicating that model D2 increased the unexplained variation between QoL scores within patients.

Model D3

$$qolscore_{ij}^{3} = \left[\left(\begin{array}{l} \gamma_{00} + \gamma_{01} emp_i + \gamma_{02} initreg1_i + \gamma_{03} initreg2_i \\ + \gamma_{10}(time_{ij}) + \gamma_{20}(hivstage2_{ij}) + \end{array} \right) + \left(\zeta_{0i} + e_{ij} \right) \right]$$

Where

qolscore	Quality of life score
emp	Employment status (employed) on recruitment
initreg1	Initial antiretroviral regimen PHAART
initreg2	Initial antiretroviral regimen NHAART
time	Time difference between questionnaire completion in monthly unit
hivstag2e	Stage of HIV infection (symptomatic and AIDS) at time j

Removal of cross level interaction between employment and time had reduced within individual variances, σ_t^2 suggesting that this removal had explained 0.2% variation between quality of life score within individual. Therefore D3 was chosen as the final model of change for quality of life.

DISCUSSION

The study found that the mean HRQoL of patients with HIV was 0.7622 (±0.2590). In the cross sectional analysis of HRQoL, three variables predicted the score of HRQoL with varying significance level at each cross section time (Table 4.9). Employment was the best predictor of HRQoL at baseline, T1 and T2 with higher HRQoL for patients in employment. Ethnicity also predicted the HRQoL score with white patients having higher HRQoL than non white patients. However, this only applied to baseline. In T3, only AIDS stage predicts the score with AIDS patients having better HRQoL than non AIDS patients.

Table 4.9 Cross section adjusted HRQoL

	T1		T2	T3
	White	Non White		
Employed	0.8292	0.7406	0.8011	
Unemployed	0.7330	0.6444	0.6865	
AIDS				0.8577
not AIDS				0.7753

The difference in predictors' significance across time illustrated the need for a longitudinal approach to HRQoL analysis, which is lacking in the past studies of preference based HRQoL measurement of HIV. There are two probable reasons for the difference.

Firstly, there was a high correlation of composite residuals (0.46) in the dataset which signalled the presence of correlation across time. This clearly violated the zero residual autocorrelation assumption in an ordinary least square (OLS) analysis used in the cross sectional multiple regression. Secondly, as was described in Table 4.5 and Table 4.6, the data were unbalanced in the sense that due to attrition, some patients' data was missing at certain time period (Wooldridge, 1999). This attrition changed the composition of sample distribution. In addition, the time difference

between questionnaire completions in the dataset varied across individuals creating an unstructured time dataset. This statistical challenge could have complicated and compromised results from conventional analysis methods, including ANOVA.

This study attempted to handle this using a longitudinal approach of multilevel model of change. One of the advantages of using a multilevel model is its ability to accommodate unbalanced panel data with unstructured time (Singer and Willett, 2003).

In the multilevel model analysis of patients' HRQoL, it was found that the uncontrolled HRQoL mean score for patients was 0.8188. In the subsequent analysis, the initial research question was explored regarding the effect of different treatment regimens on the changes in HRQoL. It was found that the type of treatment regimen that patients initially received when they first begin treatment predicted their HRQoL at baseline. Patients who had an initial treatment with non HAART regimens had the worst baseline score which equaled patients with no treatment (Table 4.10). The baseline HRQoL scores were highest for patients who had initial treatments with NHAART.

Table 4.10 Predictors of HRQoL score

Initial Regimen	Employment	Symptomatic	Initial Status	Rate of Change
PHAART	Yes	Yes	0.8804	-0.4764
PHAART	No	No	0.8245	-0.1518
NHAART	Yes	Yes	0.9006	-0.4764
NHAART	No	No	0.8474	-0.1518
no ARV/non HAART	Yes	Yes	0.8418	-0.4764
no ARV/non HAART	No	No	0.7800	-0.1518

These findings agree with previous results (Miners et al., 2001a) but contradict other studies (Delate and Coons, 2001, Gill et al., 2002), whereby this study found that

there was no relationship between HIV surrogate markers such as viral load and CD4+ count and quality of life. The study however did find that patients' HIV stage was the determinant of HRQoL's rate of change whereby the HRQoL declined faster in symptomatic patients than in asymptomatic. This echoed previous findings on the relationship between HIV stage and HRQoL (Bayoumi and Redelmeier, 1999). It also reiterated past study conclusion that short term surrogate markers such as CD4 and viral load were imperfect surrogate end points for long term clinical outcome (HIV Surrogate Marker Collaborative Group, 2000). Therefore, HIV patients need to have a direct consultation for clinical assessment of patients' health rather than depending on laboratory markers alone.

Interestingly, unlike initial treatment regimen, it was found that the treatment regimen that a patient received at the point of questionnaire completion had no linear relationship with HRQoL. The reason why initial instead of current treatment regimen affect HRQoL is uncertain. Past clinical study have shown that past exposure from antiretroviral treatment will leads to higher resistance, and more viral rebound (Easterbrook et al., 2001). From this, it could be speculated that there is a long term effect of antiretroviral treatment on patients' quality of life. The current study was limited in design to ascertain this causality and best way to do it of course would be via a prospective longitudinal study on treatment naïve patients. Regardless, these observations highlighted the importance of initial regimen as posited earlier in the thesis.

Another factor that influence the baseline HRQoL score were employment status whereby employed patients had better HRQoL than unemployed patients. This was in line with previous findings which observed the same effect in the Medical Outcomes Study Health Status Questionnaire among 200 HIV patients (Blalock et

al., 2002). One explanation for this effect is that unemployed individuals generally report more depression, anxiety, social isolation, and low self-esteem than employed individuals (Feather, 1990). In fact, unemployment was found to predict depression and suicidal ideation in HIV population (Kelly et al., 1998). Another explanation for this observation could however be simply those patients with low HRQoL can't work. This observation nevertheless suggested the need of continuous presence of social worker in the HIV multidisciplinary team as they would be responsible for patient's psychosocial need, and help alleviate the stress in unemployed patients.

SUMMARY

- Different variables predict HRQoL at different cross section time. This highlights the dynamic nature of HRQoL and inadequacy of cross sectional analysis to analyze changes in HRQoL.
- Patients' HRQoL generally decline with time.
- Baseline HRQoL score was predicted by initial treatment regimen with NHAART having higher HRQoL followed by PHAART and non HAART/no treatment.
- Another predictor of baseline HRQoL was employment whereby employed patients had better HRQoL than unemployed.
- The rate of quality of life decline was determined by HIV stage i.e. symptomatic patients' HRQoL decline faster than asymptomatic.

Chapter 5

Study III: Modeling Framework of HIV Progression

INTRODUCTION

Study II collated 24 weeks quality of life and study I collected nine years clinical and resource utilization data of the participating patients. Although this data enabled a look into the cost-effectiveness at this time period, a more appropriate endpoint for chronic disease such as HIV infection would be death. However, only one death was recorded in this study. The low mortality in patients receiving HAART was echoed in several other studies that nevertheless was a result of the effectiveness of HAART which consequently leads to unavailability of lifetime outcome experience (Raffi et al., 2001). This could hamper study usability and therefore a lifetime exploratory estimate obtainable through modelling would be more appropriate.

Recent models used to study HIV disease progression were largely Markov models. This interests lies on the fact that HIV had inherently ongoing risk over time e.g. risk of developing opportunistic illness. Consequently, there is uncertainty on the time of event occurrence which would have an important implication as utility of an outcome often depend on when it occurs (Sonnenberg and Beck, 1993). There are various ways to structure patient's progression as depicted in past models. In addition, as models needs to be informed by the appropriate empirical clinical and practical information, their developments are considered as iterative with new data informing and updating past models (Briggs and Sculpher, 1998).

The present chapter describes the development of a Markov Monte Carlo model that will be used to extrapolate and explore the cost and quality adjusted life years of HIV patients in longer time horizon and also evaluation of the cost-effectiveness of different HIV treatment strategy in study IV.

METHODS

Model Structure Description

Model Summary

A Markov Chain Monte Carlo (MCMC) simulation model was developed to assess the impact of different initial HAART treatments on HIV patient's outcome. The model structure was adapted from a previously published and validated model (Richter et al., 2002, Simpson et al., 2004). Schematic presentation of the model is illustrated in Figure 5.1.

An MCMC model is a very useful and efficient tool to depict the impact of an intervention at a detailed level in the patient's HIV progression. In this model, individual patient progression was simulated until it reached an absorption state i.e. death, whereupon another individual would be simulated. This simulation was repeated for a predefined sample size.

In the current model, simulation began with a treatment naïve HIV patient with an initial CD4+ count and viral load randomly drawn from a pre specified uniform distribution, based on the mean and standard deviation from the current study population. The patient would receive an initial HAART regimen and was assessed monthly for treatment effectiveness of viral suppression. During this time, the patient could die, or experience an AIDS defining event (ADE). In the first six months of treatment initiation, the patient would continue to receive the prescribed treatment regimen (Gazzard et al., 2006). After this time period, detectable viral load or occurrence of ADE was considered as treatment failure requiring a switch to another

treatment regimen. During the model progression, outcome of interest i.e. antiretroviral cost, chronic care cost, acute care cost and QALY were recorded for each patient. Simulation was repeated for 10,000 patients.

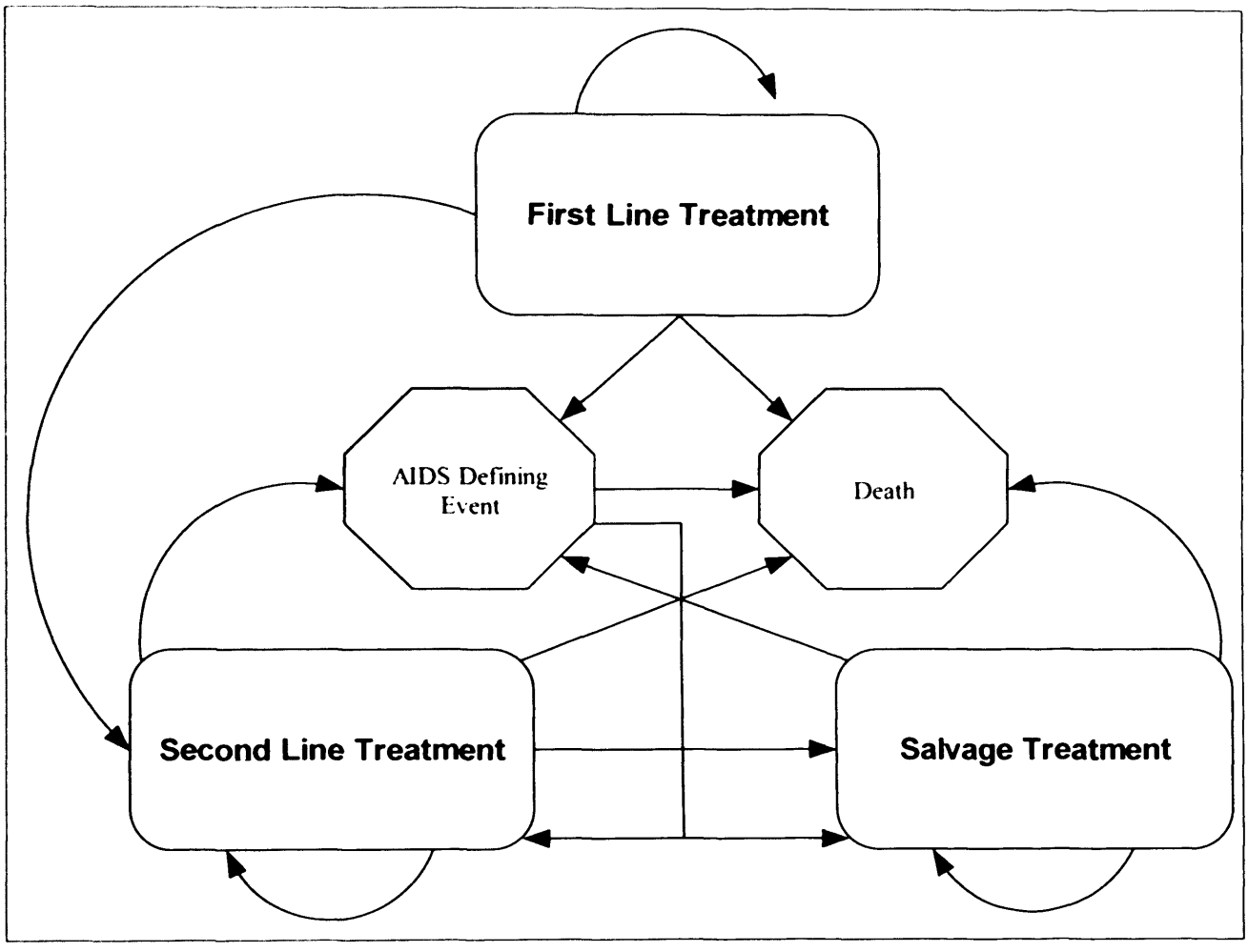


Figure 5.1 Markov-state diagrams for treated HIV patient

Progression towards Acute AIDS Defining Event and Mortality

In each cycle, patient could experience acute ADE, modelled as temporary tunnel state, for three months. This temporary state is required to assign temporarily different transition probabilities associated with acute state and also to apply a utility or cost adjustment specific to the acute state for a short cycle (Sonnenberg and Beck, 1993). The three month period was taken from the upper limit of the acute

ADE management period that ranged from 21 days to three months. In this acute ADE state, patient's still received their respective HAART regimens as the current practice and guidelines suggested (Centre for Disease Control and Prevention, 2004). At the end of the temporary state, the patient could revert back to a previous chronic state, or be considered as a treatment failure whereupon a new regimen would be prescribed depending on the duration of the current regimen, or would die from ADE. A patient was assumed to only experience one event at a time for this modelling purpose.

Several studies have demonstrated the prognostic value of CD4 count for opportunistic illness (Miller et al., 1999, Weverling et al., 1999). In the present model, patients were evaluated for the probabilities of experiencing ADE based on current CD4+ count. The probabilities of experiencing ADE were based on Richter et al (2002) estimates from a patient's longitudinal tracking database (Table 5.1).

Table 5.1 Probabilities to experience ADE

CD4+ count (cells/μl)	Monthly chance of AIDS (%)
>300	0.027
201-300	0.068
151-200	0.140
101-150	1.700
51-100	8.800
0-50	24.000

Source: Richter et al (2002)

As cost and mortality varied between ADE, patients were also modelled for specific ADE with the probabilities based on the density distribution in Simpson et al (2004) (Table 5.2).

Table 5.2 Probabilities of progression and mortality for specific ADE (n=235)

AIDS Defining Event	% of all ADE	%of all mortality from ADE
NHL	3	23.16
Cytomegalovirus	5.4	21.05
Tuberculosis	4.9	20
Pneumocystic pneumonia	13	15.79
Mycobacterium avium complex	5.8	8.42
Progressive multifocal leucoencephalopathy	1.4	6.32
Toxoplasmic encephalitis	1	2.11
Disseminated cryptococcosis	1.2	2.11
Kaposi sarcoma	4.7	1.04

Following the introduction of HAART and advances in the ADE treatment, there is a drastic change in the distribution of types of ADE and mortality rates, with less mortality from ADE being recorded (Mocroft and Saag, 2007, Martinez et al., 2007). In the present model, the mortality rate for the specific ADE is based on observation as in Martinez et al (2007).

The mortality probabilities in the chronic state are based on the prognostic value of CD4+ count from Richter et al (2002) (Table 5.3).

Besides HIV, patients' mortality is also influenced by their age, and gender. The age and sex adjusted mortality are derived from mortality table based on the United Kingdom population 2003 – 05 (Office for National Statistics (ONS), 2006).

Table 5.3 Mortality probabilities in chronic state

CD4+ cell count (cells/μl)	Chance of death within a 3-month period (%)
>100	0
45-100	0.67
31-45	1.4
16-30	2.7
01-15	3.8
0	7.2

Antiretroviral Drug Therapies

There are more than 25 antiretroviral drugs on the market for HIV infection. The current guidelines recommend NHAART based on efavirenz or PHAART based on ritonavir boosted lopinavir (LPV/r) as the first line choice for treating naïve HIV patients (Gazzard et al., 2006, Hammer et al., 2006). Although there is no large head-to-head randomized clinical trial comparing these two regimens, the efavirenz (EFV) based regimen is the more favoured option in UK. It was recently recommended in the UK guidelines as the choice for first line treatment based on two recent exploratory studies and one small clinical trial (Gazzard et al., 2006).

The rest of the HAART regimens are usually made of two NRTI drugs. Commonly prescribed NRTI combinations are tenofovir (TDF) with emcitrabine (FTC), or abicavir (ABC) with lamivudine (3TC) or zidovudine (AZT) with lamivudine (3TC). 3TC with AZT had been the recommended first line backbone but is now no longer recommended. This was because of links between anaemia, fatigue and lipoatrophy reactions with AZT. Other NRTI such as stavudine (d4T) and didanosine (ddI) are also no longer recommended due to its lipoatrophy effect and difficulty with administration.

In the present model, PHAART based on ritonavir boosted lopinavir was compared with NHAART based on efavirenz (Table 5.4).

The initial regimen composition was based on the original regimen composition compared in the only RCT to date with lamivudine and zidovudine as the backbone pair of choice (Riddler et al., 2006). Subsequent regimen selection was based on recent practice and the principle of substituting at least two (preferably three) active drugs from the failed regimen (Gazzard et al., 2006).

Table 5.4 Treatment plan with its associated efficacy

Treatment group	Therapy	Weeks of data available	Maximum achieving full suppression (<50cp/mL)		Uniform distribution for time to failure		CD4+ cell count gain with successful therapy
			%	time (wk)	min	max	
1 PI + 2 NRTIs	LPV/r + 3TC + AZT (1st Line)	96	77[a]	96	24[e]	512[e]	285[a]
1 NNRTI + 2 NRTIs	EFV + FTC + TDF (2nd Line)		62[e]		72[e]	481[e]	110[e]
1 PI + 2 NRTIs	ATZ + ddC + ddI (3rd Line)	48	44[b]	48	24[e]	512[e]	110[b]
1 NNRTI + 2 NRTIs	EFV + 3TC+ AZT (1st Line)	96	89[a]	96	72[e]	481[e]	239[a]
1 PI + 2 NRTIs	LPV/r + 3TC + AZT (2nd Line)		54[e]		24[e]	512[e]	110[e]
1 NNRTI + 2 NRTIs	NVP + 3TC + ddI (3rd Line)		21[c,e]		72[e]	481[e]	110[e]

Source: [a]Riddler et al (2006);[b]Johnson et al (2005);[c]van Leth et al (2004);[e]estimate

Past models had assumed that treatment was stopped as soon as treatment options were exhausted (Richter 2002). However, it has been recommended that patients continue to receiving failing treatment (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006). As current practice had adopted this recommendation, the present model allows patients to continue receiving third line failing treatment and also continues modelling the markers change during this period (Cozzi-Lepri et al., 2003)

Treatment Effectiveness

HIV treatment effectiveness is multifactorial and each factor interacts with one another in a different way. An example would be the interaction between adherence and resistance whereby improved adherence was found to reduce the resistance of

the virus towards protease inhibitors but increased the resistance to non nucleoside reverse transcriptase inhibitors (Bangsberg et al., 2006).

As a model is meant to simplify a complex real world situation, the factors can be simplified by determining treatment effectiveness to be a function of multiplicative interaction between resistances, expressed by a randomly sampled time to failure, and regimen efficacy that would give the probability of viral load suppression in one cycle.

The efficacy for each treatment was derived from intention to treat analysis (ITT) in multiple sources based on best evidence available and decision analysis of best practice (Philips et al., 2004, Weinstein et al., 2003). Table 5.4 shows details of efficacy estimates for each regimen.

There has been no large published randomized clinical trial of head to head comparisons between EFV and LPV/r as initial regimens. After a systematic literature search, only five observational studies and two small RCT were highlighted (Domingo et al., 2006, Riddler et al., 2006, Echeverria et al., 2006, Pulido et al., 2006, Torti et al., 2005).

All the studies agreed that EFV based regimens have a better viral suppression rate than LPV/r based regimens, though the latter has better immunological improvement. For the current model, results from Riddler et al. (2006) were used for baseline analysis as the study had a longer time period and larger sample size compared to the Pulido et al (2006).

There has been a considerable lack of evidence for efficacy of subsequent regimen after initial regimen failure. Atazanavir (ATZ) has been investigated in multiple virologic failure patients and was found to have a similar efficacy with LPV/r but with a better safety profile (Johnson et al., 2005). It has been widely adopted in the

current study practice setting and is therefore included as a third line regimen in patients with initial PHAART.

The paucity of evidence in similar circumstances for other regimens has led to the adoption of an empirical estimate in Richter et al (2002) and Simpson et al (2004) that assumed the virological efficacy for second line regimens was reduced by 70% and 30% for the third line regimens. This reduction was applied to efficacy estimated in treatment naïve patients for nevirapine (NVP), LPV/r, and EFV based regimens (van Leth et al., 2004, Riddler et al., 2006).

The distribution of time to failure was adapted from Richter et al (2002) who estimated the probability of continued viral suppression following the point in time at which the maximum percentage of patients achieved viral suppression. This was done by dividing the observed percentage of patients achieving viral suppression by the maximum percentage who achieved viral suppression.

Surrogate Markers Change

The first viral load at treatment initiation was considered as a viral set point. Successful treatment would suppress the viral load to an undetectable level after six months. Immune recovery is found to be faster in patients receiving PI than NNRTI (Barreiro et al., 2002b, van Leeuwen et al., 2003, Riddler et al., 2006). The immunological improvement rate in Riddler et al (2006) was applied to initial HAART treatment success. Subsequent regimens for immunological improvement were assumed to be the same as that found for ATZ based regimens by Johnson et al (2005) following observation of no differences for immunological improvement in compared regimens. This was however more pessimistic than other model

assumptions that the improvement was in the range of 30 – 50 cells/mm^3 (Richter et al., 2002, Simpson et al., 2004).

If the treatment was unsuccessful, the viral load would remain at its set point. The CD4 count would decline monthly with each failure based on viral load count (Freedberg et al., 2001) (Table 5.5). If it was unsuccessful for 6 consecutive months, the treatment was considered to have failed and a subsequent line of treatment would be initiated (Gazzard, 2005).

Table 5.5 Mean monthly decline of CD4 count according to HIV RNA level

HIV RNA (copies/mL)	Decline in CD4 count (cells/mm3)
>30,000	6.375
10,001 - 30,000	5.4
3001 - 10,000	4.6
501 - 3000	3.733
≤500	3.025

It was recommended that a patient who had exhausted all treatment options should continue receiving failing treatment until a new option became available. This recommendation was implemented in the present model by modelling the markers change during this period (Cozzi-Lepri et al., 2003). Cozzi-Lepri et al (2003) had estimated that the viral load increased by 0.024 $\log_{10}$ copies/ml per month and CD4+ cell reduced by 0.53 cells/μl per month. Markers changed for patients that failed all regimens and who were already receiving a third line regimen based on observation that immune recovery slowed after first month and unchanged after two years (Smith et al., 2003).

To date, there have been no published studies that evaluate changes in surrogate markers during acute illness. However, there have been a few studies that

observed comparable virological and immunological changes for patients with treatment initiated during acute or early HIV-1 infection (Kassutto et al., 2006). Therefore, in the present model, it was assumed that patients would have equivalent virological and immunological changes in both chronic and acute stages.

Cycle Length and Time Horizon

The cycle length chosen needed to represent a clinically meaningful time interval. The interval chosen needed to reflect the disease natural history, and this was chosen as monthly. The model would be run for three time periods i.e. three years, five years and fifty years. Half cycle correction was not needed as this model time horizon was considerably large (Sonnenberg and Beck, 1993).

Model Calibration and Validation

As with any model that derived data from multiple sources and simplified real process, the current model needed to be verified for its consistency and validity (Weinstein et al., 2001). In this study, internal consistency of the model was evaluated by setting the mortality probability to zero. The results from simulation of this change should give the number of death to be zero. The model was also validated for convergent validity by comparing its output against Richter et al (2002) model output that had previously been successfully validated. Face validity of the model was assessed by comparing its output of survival between no treatment options and initial PHAART. For this purpose, the model was simulated for natural HIV progression in 10,000 hypothetical HIV symptomatic patients.

RESULTS

As a result of the above consideration, a Markov Monte Carlo simulation model was developed and outlined as in Appendix VII. The model depicts the choice of initial regimens between PHAART and NHAART and also a no treatment option as the validity benchmark. Randomly drawn patients from 10,000 hypothetical samples would run through the simulation until death or the simulation terminated.

This model was simulated from 10,000 patients with mean initial CD4+ count of 170 cells/mm^3 (SD=135) and a mean viral load of 2.30E+06 copies/ml (SD = 2.50E+05). Model was first simulated for mortality of untreated patients. The results were plotted in Figure 5.2.

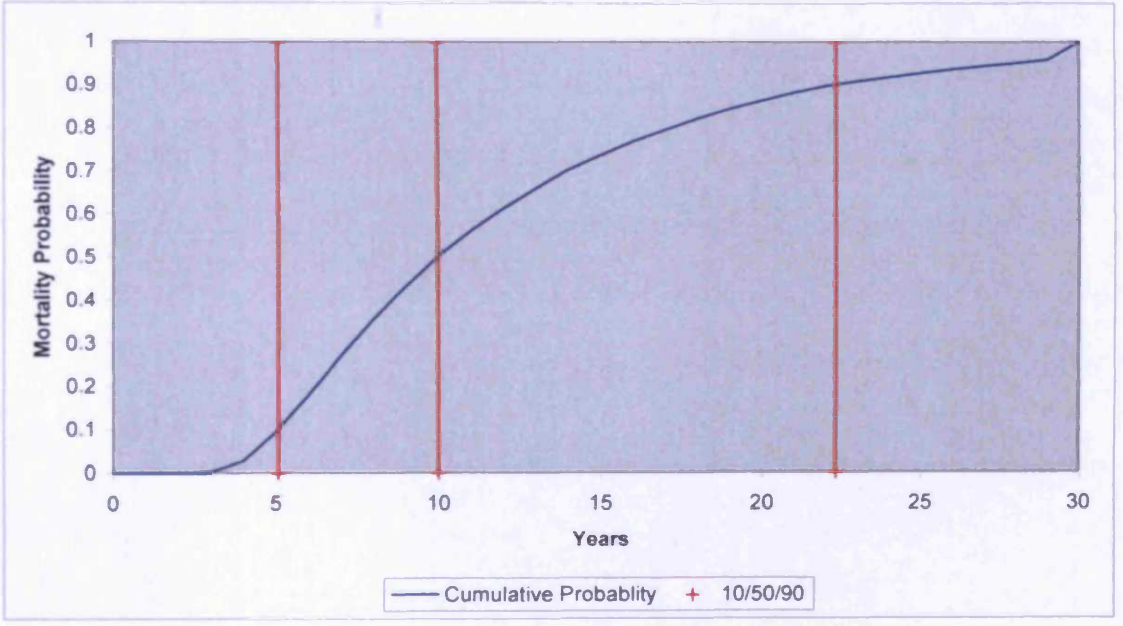


Figure 5.2 Probability of death for patients with no treatment (present model)

This was compared to the curve obtained from model output in Richter et al (2002). It should be noted however that the curve (Figure 5.3) from Richter et al (2002) was

a survival curve that shows the probability of survival at the shown time whereas the present model output was plotted as probability of death within shown time.

The curve obtained in the present model behaved in almost similar way in the first eight years with the compared curves whereby patients have zero probability of death within the first four years. The probability of death declined at almost the same time (after eight years) for both curves with a mean life expectancy of 5.46 years (SD = 3.86). However, the maximum life expectancy differed between the two models' output. The maximum life expectancy estimated in the present model was 35 years whereas Richter et al (2002) gave a maximum of 15 years life expectancy.

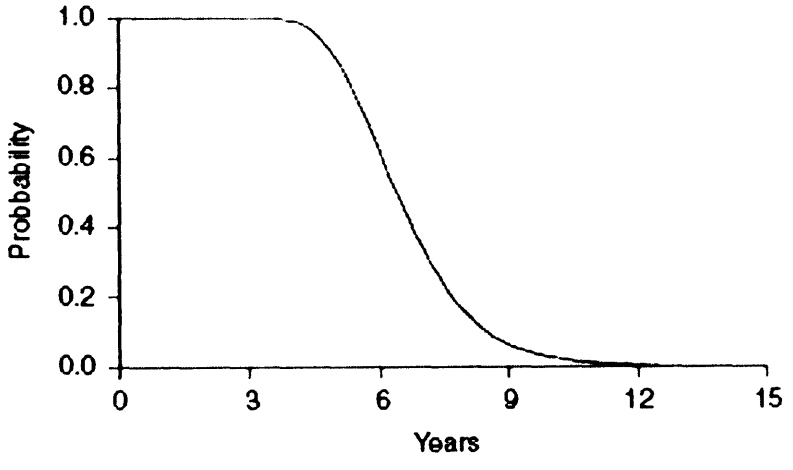


Figure 5.3 Survival probabilities for patients with no treatment (Source: Richter et al, 2002).

The model was simulated for face validity by comparing no treatment with treated patients. The results of simulation for patients treated with initial PHAART were plotted in Figure 5.4. In comparison to untreated patients in Figure 5.2, the treated patients had lower probability to death and longer life expectancy than untreated patients.

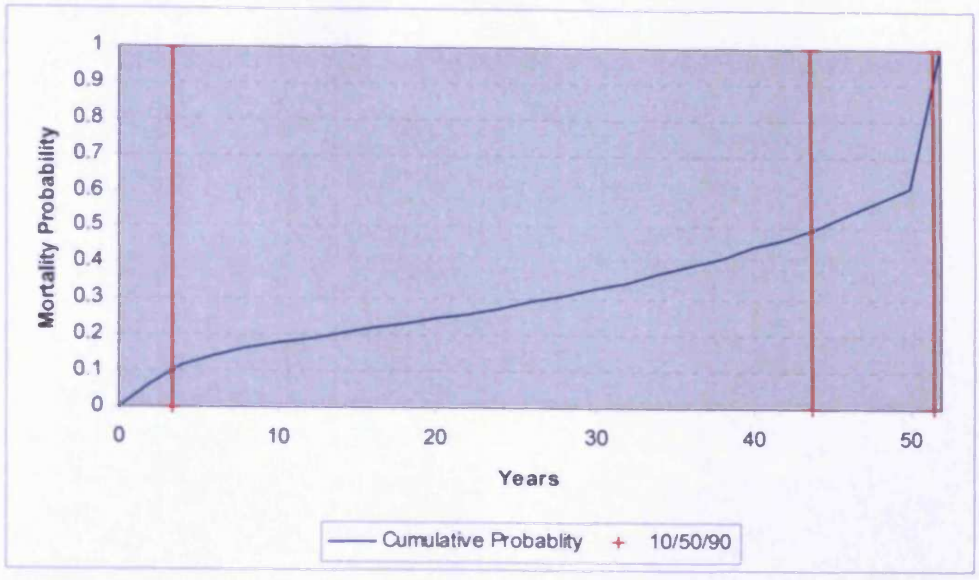


Figure 5.4 Probability of death for patients with initial PHAART

DISCUSSION

This chapter describes the development of Markov Monte Carlo simulation model of HIV patient progression. This would allow evaluation of initial antiretroviral treatment effect on patients' intermediate and final outcome (treatment failure, acute AIDS defining event, death) required in Study IV. The developed model enabled simulation of a number of hypothetical patients with randomly drawn CD4+ count and viral load. The outcomes of the simulation were dependent on patient surrogate markers (CD4+ count and viral load) which changed at each cycle.

The model was assessed for convergent and face validity in this chapter. The validation demonstrated the model's ability to provide adequate depiction of HIV progression. However, through this validation, it was found that the model could also provide a questionable output on a longer time horizon based on the observation that there were still patients surviving even after 20 years of no treatment. In contrast, patients were expected to have a maximum life expectancy of 15 years in

a previous study (Richter et al., 2002). Therefore, earlier time horizons i.e. three and five years should also be evaluated in its further application.

In the present model, several key assumptions had to be made during its development. Firstly, it was assumed that patients experienced only one ADE at a time. This assumption would underestimate the interaction between ADE or co morbidity seen in practice but this simplification is necessary due to the limitations of using incidence density rates to model the risk of specific ADE.

Secondly, it was assumed that patient likelihood of acute ADE or death was conditional on CD4+ count (Ghani et al., 2001a, Ghani et al., 2001b). This was in contrast with previous HIV models (Caro et al., 2001) that incorporated the effect of both viral load and CD4+ count in determining likelihood of survival or experiencing acute ADE. Although viral load and CD4+ count was previously documented (Mellors et al., 1997) to provide prognostic value of HIV progression, recent evidence found that in patients receiving HAART, viral load could not provide sufficient accountability of treatment effect (Smith and Stein, 2002).

Finally, the patient was assumed to only have two treatment switches with the simplest management form i.e. maintaining last failing regimen. In practice, management of patients in salvage treatment is more complicated with the consultant often experimenting with structured treatment interruption (STI) strategies, nucleoside cycling, and MegaHAART (combination of more than five agents).

Though it's tempting to incorporate all treatment practice in a model, in the end, a model is only a simplification of real life. A highly complex model would not only complicate results, but also lead to 'black box syndrome' whereby the model would be too complicated to understand resulting in it being ignored.

The present model was developed based on previous models (Richter et al., 2002, Simpson et al., 2004), and also on best evidence and practice available (Weinstein et al., 2003, Garrison, 2003). There are considerable lacks of studies comparing different HAART regimens. The model developed will add to the understanding of the effect of different HAART regimens particularly initial treatments on patient outcomes.

SUMMARY

- A Markov Monte Carlo model was developed to simulate HIV progression for 10,000 randomly drawn hypothetical patients.
- The patients were symptomatic with a randomly drawn viral load and CD4 count.
- The model evaluates the long term effect of initial therapy on HIV patient progression through HIV stages. It began with a symptomatic treatment-naïve patient in a chronic state that had been initiated with a HAART regimen. Health regression or progression into acute AIDS defining state or death would follow, depending on treatment outcome and surrogate markers CD4+ that were updated at each cycle (monthly).
- The model developed demonstrated good validity in comparison with survival estimates seen in past studies.

CHAPTER 6

Study IV: Lifetime Cost-effectiveness and Utility Analysis

INTRODUCTION

In Study I and II (Chapter 3 and 4), choice of initial highly active antiretroviral (HAAART) regimen was found to significantly affect patient's chronic outpatient cost and health related quality of life (HRQoL). This finding however was limited in its general and long term application due to its short follow up and low event (AIDS defining event or death) rate. This echoed the issues faced by clinical studies that had to rely on intermediate or surrogate markers instead of the patients' final outcome (De Milito et al., 2003).

Deferring the selection of optimal initial regimen combinations until more definitive long term evidence is published however could lead to unnecessary delay of benefit or resource omission error. On the other hand, making a decision with insufficient long term evidence could result in wasted resources or even harm patients if a more costly or less effective treatment is chosen (Weinstein et al., 2001).

Modeling techniques that could synthesize available evidence to extrapolate the final outcome is gaining acceptance as an aid to decision and policy makers in the absence of definitive long term evidence. This technique is also invaluable in any economic analysis that needs a systematic approach to evaluate both cost and benefits of the choice.

Therefore, in order to explore the long term effect of initial regimen on the outpatient cost and HRQoL, the preceding chapter conceptualized, validated and calibrated a Markov Chain Monte Carlo (MCMC) of HIV patient's clinical and therapeutic progression. The current chapter aims to explore the cost and health related quality of life of patients with HIV in a longer time horizon through this model. In addition, the choice of initial HAART regimen combinations was evaluated using economic evaluation tools for the choice that could maximize benefit given limited resources.

METHODS

Model Summary

A Markov Monte Carlo (MCMC) was developed for HIV patient progression. Details of the structure, transition probabilities and assumption were described in the previous chapter.

In short, the model simulates the disease and treatment progression of an individual HIV patient in a Markov framework with varying risks of death and AIDS defining illness over time modified by treatment intermediate outcomes. Each of the health states is associated with specific costs and quality of life weightings that contribute to the patient's final cumulative cost, survival and quality adjusted life years (QALY) and consequently to the cohort's mean cost and benefit.

Comparator

In the present study, the model was used to compare the clinical, economic and humanistic outcomes between treatment naïve patients who received initial treatments of PHAART consisting of ritonavir boosted lopinavir (LPV/r), lamivudine (3TC) and zidovudine (AZT) in comparison to patient's that received the current UK physician's preferred initial treatment of NHAART consisting of efavirenz (EFV), emcitrabine (FTC), and tenofovir (TDF).

These combinations were chosen based on the current guidelines recommendations and on clinic practice (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006, Gazzard et al., 2006). The dosage for each combination was given in Table 6.1. No treatment option was used to validate the results.

Patients

10,000 hypothetical patients were simulated in the model. At initial simulation run, patients were treatment naïve, of adult age, and in the symptomatic stage of HIV. CD4+ count, viral load, and age of patient were randomly drawn from a uniform distribution at each simulation.

Time Horizon

The model cycle length was one month to reduce variance as results of varying rates of surrogate markers progression and patient's resource utilization.

Analysis was done at four time horizons to allow flexibility in interpretation of results: three years, five years, ten years and lifetime (i.e. when every simulated patient had died).

Discounting

Discounting is an important consideration in a long time horizon study such as the present study that seeks to simulate a lifetime estimate of treatment effect. It refers to the desire to enjoy benefits in the present while deferring any negative effects of doing so. A more detailed discussion of discounting is presented in Chapter 2. Results were therefore presented both as undiscounted and discounted in this study. The baseline analysis was based on results from discounted cost.

Following suggestions in the UK guidelines, only cost that was accrued beyond one year was discounted at 3 % (Drummond and Jefferson, 1996).

Rewards

The outcomes of the model are accumulation of rewards that incremented at each model cycle by each patient. The rewards were components of the study overall outcome of interest i.e. costs, life expectancy, and quality adjusted life years (QALY).

Cost

The total cost per patient includes the outpatient care cost, cost of antiretroviral treatment and cost of treating acute AIDS defining event (ADE). Medication cost for prophylaxis and adverse drug treatment was not included.

Antiretroviral

The cost of an antiretroviral regimen was derived from the recommended standard dose for adults weighing over 40kg, using standard UK drug prices (Table 6.1) (Joint Formulary Committee, 2007).

Table 6.1 Monthly cost of antiretroviral regimen

SEQUENCE	REGIMEN	DOSE	MONTHLY COST (£)
1ST Line	LPV/r + 3TC + AZT	LPV/r[a]: 400mg/100mg BD 3TC /AZT[b]: 150mg/300mg BD	584.26
2ND Line	EFV + FTC + TDF	EFV[c]: 600mg OD FTC/TDF[d] 200mg/245mg OD	585.11
3RD Line	ATZ/r + ABC + 3TC	ATZ[e]: 300mg OD Ritonavir[f]: 100mg OD ABC/3TC[g]: 600mg/300mg OD	706.55
1ST Line	EFV + FTC + TDF	EFV[c]: 600mg OD FTC/TDF[d]: 200mg/245mg OD	585.11
2ND Line	LPV/r + 3TC + AZT	LPV/r[a]: 400mg/100mg BD 3TC /AZT[b]: 150mg/300mg BD	584.26
3RD Line	NVP + NFV + ABC + 3TC	NVP[h]: 200mg BD NFV[i]: 1.25mg BD ABC[j]: 300mg BD 3TC[k]: 150mg BD	753.29

a=Kaletra™; b=Combivir™; c=Sustiva™; d=Truvada™; e=Reyataz™; f=Norvir™; g=Kivexa™; h=Viramune™; i=Viracept™; j=Ziagen™; k=Epivir™

Chronic Outpatient Care

In the previous chapter, the chronic monthly cost per patient could be given as a function of nationality, time, initial regimen, age, CD4+ count, HIV stage and viral load by the following equation:

$$lncost_{ij} = \left[\begin{array}{l} \left(5.087 - 0.213(nat_i) + 0.002(time_{ij}) + 0.156(initreg1_{ij}) + \right. \\ \left. 0.167(initreg2_{ij}) - 0.009(age_{ij}) + 0.086(cd4cat1_{ij}) + \right. \\ \left. 0.115(cd4cat2_{ij}) + 0.148(vlcat1_{ij}) + 0.147(hivstage2_{ij}) \right) \\ + \left(\zeta_{1i}(time_{ij}) + \zeta_{0i} + e_{ij} \right) \end{array} \right]$$

where

lncost	Natural log of outpatient care monthly cost
time	Time in monthly unit
age	Age of patient
cd4cat1	Categorization of CD4+ count <250 at time j
cd4cat2	Categorization of CD4+ count 250 - 500 at time j
vlcat1	Categorization of viral load <1000 at time j
initreg1	Initial antiretroviral regimen (PHAART)
initreg2	Initial antiretroviral regimen (NHAART)
hivstage2	Stage of HIV infection (AIDS) at time j
nat	Nationality (British) on recruitment

Therefore, the adjusted chronic outpatient care cost per patient per month by initial regimen was calculated as in Table 6.2.

Table 6.2 The chronic outpatient care cost per patient per month

		British			Non British		
VL	CD4	No Treatment	PHAART	NHAART	No Treatment	PHAART	NHAART
<1000	<200	£191.52	£223.86	£226.33	£236.99	£277.00	£280.06
	201 - 500	£197.16	£230.44	£232.99	£243.96	£285.15	£288.30
	>500	£175.74	£205.41	£207.68	£217.46	£254.17	£256.98
>1000	<200	£165.17	£193.06	£195.20	£204.38	£238.89	£241.53
	201 - 500	£170.03	£198.74	£200.94	£210.40	£245.92	£248.64
	>500	£151.56	£177.15	£179.11	£187.54	£219.20	£221.63

Table 6.3 Cost of acute AIDS defining event (ADE) per patient per event

AIDS Defining Event	Cost 2002 US$	Cost 2005 £
NHL	$86,798.00	£55,441.81
Cytomegalovirus	$192,311.00	£122,837.74
Tuberculosis	$20,302.00	£12,967.81
Pneumocystic pneumonia	$5,027.00	£3,210.97
Mycobacterium avium complex	$65,953.00	£42,127.17
Progressive multifocal leucoencephalopathy	$24,203.00	£15,459.55
Toxoplasmic encephalitis	$30,550.00	£19,513.67
Disseminated cryptococcosis	$35,834.00	£22,888.80
Kaposi sarcoma	$5,407.00	£3,453.70
Other ADE	-	£76.00

Acute Episode

Fatal ADE costs were derived from Simpson et al (2004) which gives an estimate of acute costs based on Medicaid bills in 2002 US dollars (Simpson et al., 2004). This cost was inflated to 2005 UK pounds sterling based on the Gross Domestic Product (GDP) deflator (Officer and Williamson, 2006) (Table 6.3). Other non fatal ADE costs were based on UK NHS reference costs estimate (Department of Health, 2005b).

Utility

The utility of the patient in a chronic state was based on the quality of life score that was previously modelled as a function of employment, initial regimen, time and HIV stage in Chapter 5 as the following:

$$qolscore_{ij}^{3} = \left[\left(\begin{array}{l} \gamma_{00} + \gamma_{01} emp_i + \gamma_{02} initreg1_i + \gamma_{03} initreg2_i \\ + \gamma_{10}(time_{ij}) + \gamma_{20}(hivstage2_{ij}) + \end{array} \right) + \left(\zeta_{0i} + e_{ij} \right) \right]$$

Where

qolscore Quality of life score
emp Employment status (employed) on recruitment
initreg1 Initial antiretroviral regimen PHAART
initreg2 Initial antiretroviral regimen NHAART

time Time difference between questionnaire completion in monthly unit
hivstage2 Stage of HIV infection (symptomatic and AIDS) at time j

This gave the utility for each patient, with an assumption of constant rate, as in Table 6.4. However, as the model only captures quality of life in the chronic state, the utility of the patient in the acute state was derived from an external study standard gamble estimate of HIV patients in major ADE (Bayoumi and Redelmeier, 1999).

Table 6.4 Utility of HIV patients

	QoL
Initial PHAART	0.724
Initial NHAART	0.745
no HAART	0.686
Acute	0.410

The utility was multiplied against the length of time a patient spent in a specific health state to give quality adjusted life years (QALY).

Analysis

The simulated cost, life expectancy and QALY were compared numerically and graphically at 3 years, 5 years, 10 years and lifetime. In addition, the cost was analyzed individually to provide a picture of the influence of each component cost towards total cost.

The incremental cost-effectiveness ratio (ICER) was compared between patient's that received PHAART as an initial regimen and patient's that received NHAART. This was calculated as:

$$ICER = \frac{(\text{Total Cost PHAART - Total Cost NHAART})}{(\text{Effectiveness PHAART - Effectiveness NHAART})}$$

Parameter uncertainty was analyzed using one way parameter sensitivity analysis and probabilistic sensitivity analysis with the willingness to pay threshold set at £30,000/QALY.

RESULTS

The total discounted cost and life expectancy (LE) for patients that received PHAART as the initial regimen was £255,905.80 (SD = £110,000) and 34.68 years respectively (Table 6.5). This was lower than that observed in patients that received NHAART (£268,325.72 (SD = £110,000); 35.46 years). In fact, patients that received NHAART had a higher cost than PHAART at all time horizons except in the first five years whereby patients with initial NHAART had a slightly lower cost than patients with PHAART. The undiscounted total cost was analyzed for contributions from component cost i.e. antiretroviral and chronic outpatient cost in lifetime exploration. Antiretroviral costs made up the majority of the total costs, from 63% in patients with initial PHAART to 65% in initial NHAART patients. Outpatient costs contribute less than 20% of the total costs. This implied that cost of treating ADE was less than 15% of the total costs.

The total lifetime cost of antiretroviral regimens including the cost of the initial regimen, second line regimen, and third line (salvage) regimen in patients with an initial regimen of NHAART was more than three times the cost of outpatient care. The antiretroviral cost was however only double the outpatient's costs in patients that received PHAART as an initial regimen. Patients that received NHAART as an

Table 6.5 Undiscounted and discounted cost and effectiveness (British patients)

TIME HORIZON		3		5		10		LIFETIME	
REGIME		Mean	SD	Mean	SD	Mean	SD	Mean	SD
No ARV	Undiscounted Cost	£42,391.08	£58,235.26	£73,666.82	£80,701.89	£129,466.91	£123,766.78	£221,208.81	£211,948.99
	Discounted Cost	£35,153.06	£51,460.13	£60,267.83	£70,053.52	£103,020.45	£102,370.61	£155,969.31	£140,115.78
	LE	2.78	0.58	4.28	1.29	7.04	3.26	11.79	10.47
	QALY	1.81	0.41	2.82	0.87	4.61	2.22	7.76	7.12
PHAART	Undiscounted Cost	£48,021.76	£41,601.75	£74,467.88	£48,581.73	£129,960.23	£61,632.38	£455,157.54	£221,614.91
	Discounted Cost	£41,449.74	£34,293.06	£63,907.16	£41,280.40	£107,834.37	£51,157.19	£255,905.80	£110,938.80
	LE	2.87	0.49	4.63	1.06	8.89	2.67	34.68	17.94
	QALY	1.99	0.35	3.27	0.75	6.33	1.93	24.96	12.97
NHAART	Undiscounted Cost	£47,370.81	£39,657.42	£74,201.36	£46,252.95	£132,233.67	£59,435.69	£481,262.16	£223,809.57
	Discounted Cost	£40,725.70	£32,090.40	£63,776.17	£38,462.16	£110,019.64	£49,207.46	£268,325.72	£110,055.16
	LE	2.88	0.47	4.67	1.01	9.01	2.55	35.46	17.53
	QALY	2.06	0.35	3.39	0.74	6.61	1.89	26.36	13.02

Table 6.6 Lifetime cost breakdown

	Outpatient		ARV	
	Mean	SD	Mean	SD
No Treatment	£19,659.96	£19,582.56	-	-
PHAART	£82,221.58	£41,492.53	£285,447.85	£148,040.64
NHAART	£84,993.89	£41,135.24	£311,012.91	£154,603.15

initial regimen also had higher outpatient care costs (20%) and antiretroviral costs (9%) in comparison to patients that received PHAART as an initial regimen.

Survival of patients receiving HAART was extended by more than 20 years compared to patients not receiving any treatment, demonstrating the face validity of the model. In comparison, between the two initial regimen choices, life expectancy (LE) was higher in patients with initial NHAART at all times with one year difference from ten years onwards. A similar trend was seen for QALYs whereby they were consistently lower for patients with initial PHAART regimens in comparison with NHAART regimens. The magnitude of the QALY difference however was only more apparent in the lifetime horizon. In shorter time horizons, the difference was less than 0.5 QALY.

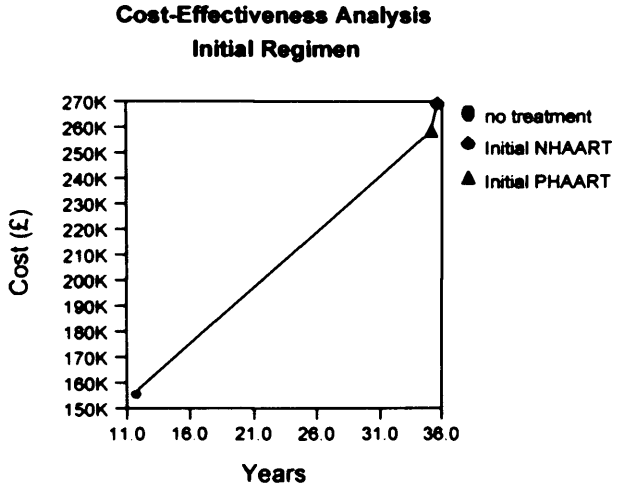
Efficiency

A cost-effectiveness graph was plotted in Figure 6.1a. The plot shows that patients receiving initial NHAART had a longer life expectancy but was also more costly than initial PHAART. When cost was plotted against QALY, NHAART as initial regimen was also more costly and had higher QALYs than initial PHAART (Figure 6.1b). The no treatment option was both less effective and less costly than the treatment option in both cost-effectiveness graphs.

The slope of the line connecting two cost-ordered treatment options gives an ICER, which is the ratio of mean incremental cost and mean incremental effectiveness (£/LY or £/QALY gained). This would give an ICER of initial NHAART in comparison to PHAART as £21,671.65/LY and £8,871.37/QALY gained for CEA and CUA respectively. However, as NHAART was more costly and effective than PHAART, the choice was not straight forward.

One way to aid decision-making is to plot points representing each ICER for all iterations in the simulation for NHAART (chosen as comparator now as it was determined to be both more costly and effective) relative to a baseline (PHAART).

a)



b)

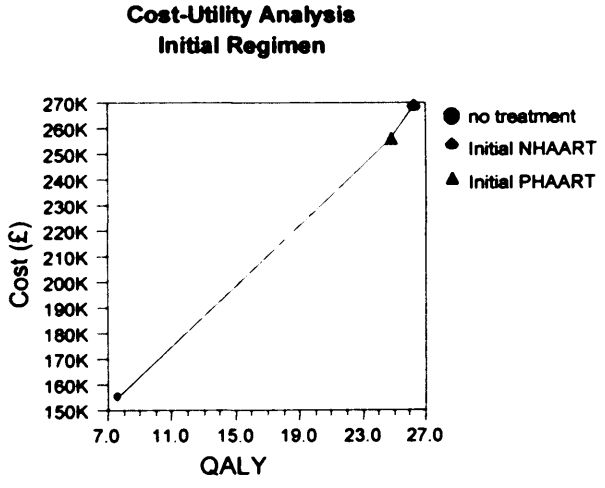


Figure 6.1 Cost-effectiveness graph for initial regimen

This was plotted as incremental cost-effectiveness (ICE) isocontours density plot as in Figure 6.2. The ICE isocontours graph shows the relative concentration of points in a scatterplot, using a range of colors/shades to indicate regions of different

concentration. The dotted diagonal line represents the ICER or cost-effective threshold of £30,000.

In this graph, the plot was more spread in CEA (Figure 6.2a) than CUA (Figure 6.2b) accommodating both second (North-West) and third (South-West) quadrants of the graph which means either the PHAART was less costly and effective or it was more costly and effective than NHAART respectively. In either case, the PHAART was the optimal choice based on the threshold of £30,000. Initial PHAART was also a more cost-effective choice in CUA based on this threshold.

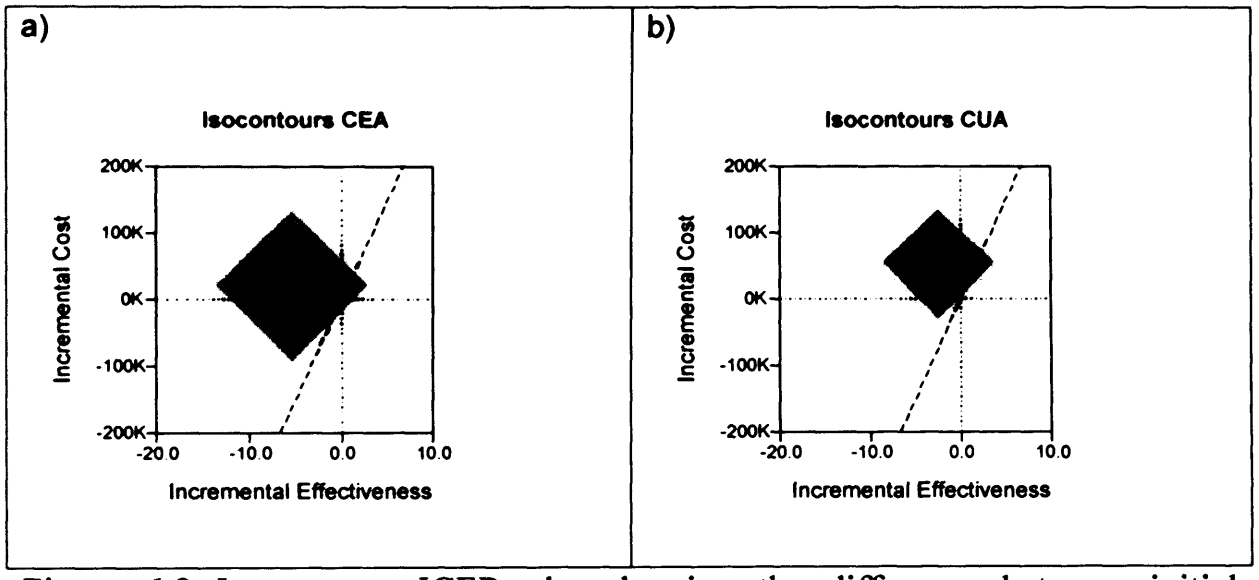


Figure 6.2 Isocontours ICER plot showing the difference between initial NHAART with initial PHAART for all iterations.

Sensitivity Analysis

The results for one way sensitivity analysis in Figure 6.3 shows that the model was quite robust towards change in quality of life (0.3 – 0.9), cost of outpatient care (£100 - £1000/month) and efficacy of third line treatment regimen (Figure 6.3).

However, the results show slight positive sensitivity towards change in the first line probability of viral suppression.

The effects of varying the cost-effectiveness threshold were investigated in the cost effectiveness acceptability curve (CEAC) in Figure 6.4. CEAC gives the probability that a treatment is cost-effective as the proportion of times the treatment is preferred from the results of 10,000 simulations at different thresholds. Initial treatment with PHAART was 70% more cost-effective in cost-effectiveness analysis compared to initial treatment with NHAART at all willingness to pay thresholds.

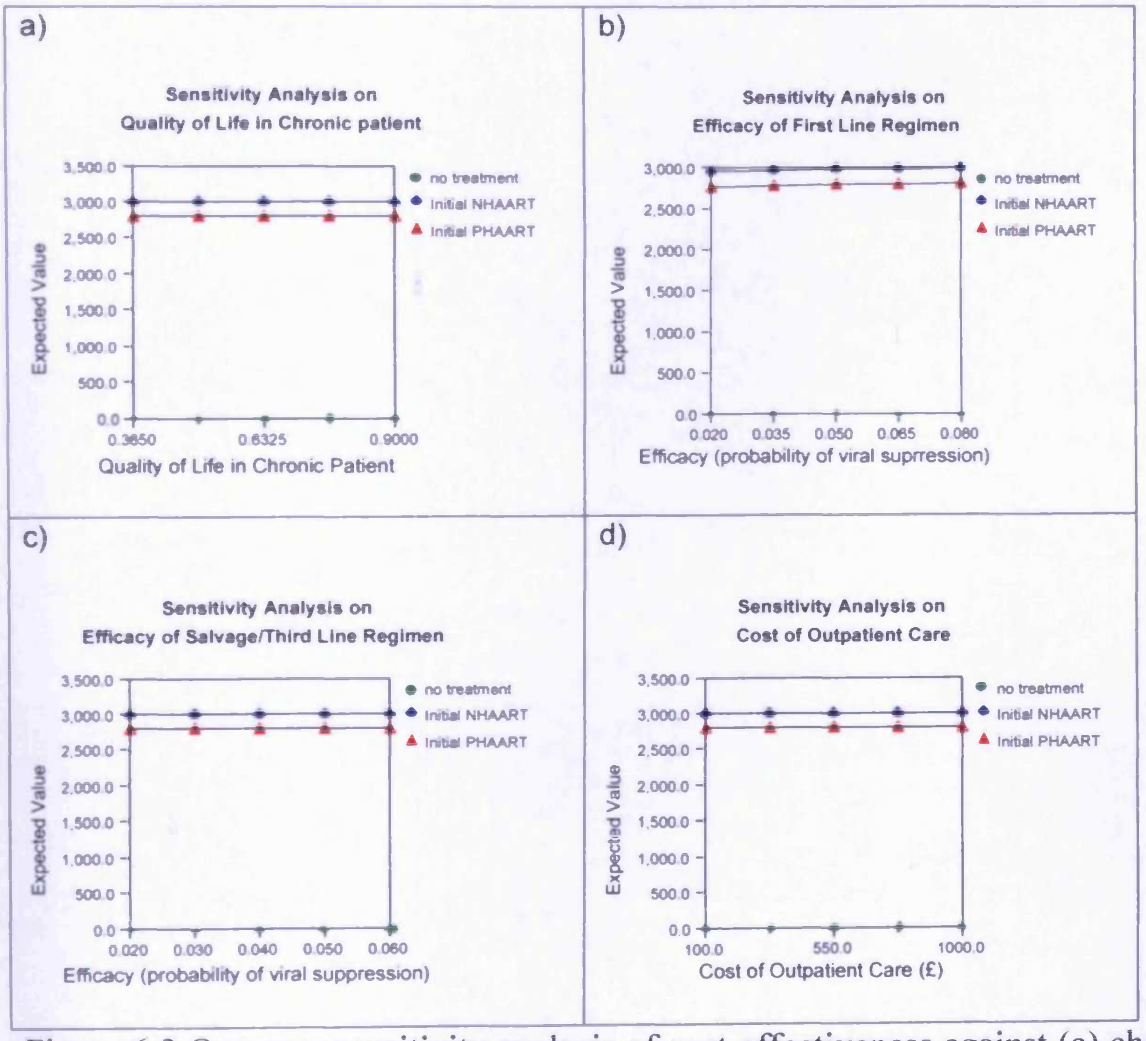


Figure 6.3 One way sensitivity analysis of cost-effectiveness against (a) change in quality of life in chronic patients (b) efficacy of first line regimen (c) efficacy of salvage regimen and (d) cost of outpatient care.

However, in cost utility analysis, the results were not as straight forward. Initial regimen with PHAART was more cost-effective at the £10,000/QALY threshold but its probability of cost-effectiveness started declining until it reached the willingness to pay threshold of £25,700/QALY.

From that point onwards, initial regimen with NHAART was more cost-effective than PHAART in the lifetime period. Initial NHAART also was the favoured option in more than 50% of the simulation results. The CEAC for CUA also shows that at threshold or willingness to pay of £0, i.e. when only cost matters, PHAART was the preferred choice. However, moving the threshold towards infinity where only effects matter, NHAART was the preferred choice.

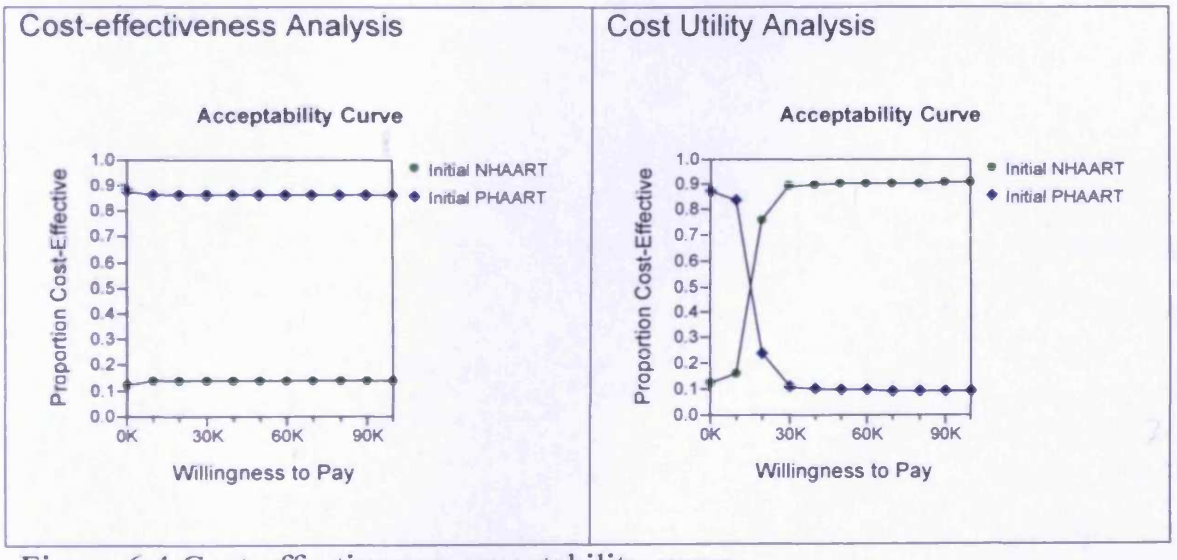


Figure 6.4 Cost-effectiveness acceptability curve

DISCUSSION

In order to understand the effect of initial HAART regimens, this study sought to extrapolate the results from the previous longitudinal analysis on cost and quality of life in a longer time horizon. This was achieved through simulation in a newly developed Markov Chain Monte Carlo model that simulates patient clinical

progression to AIDS defining event and death and also treatment progression with varying risk viral suppression rates and regimen sequencing. The total cost and effectiveness from the lifetime model were cumulative outcomes from patient's clinical and economic experiences until death.

In the baseline analysis, the cost for patients with initial NHAART was 0.25% lower than initial PHAART only up to the first five years of patient's treatment. Henceforth, a patient who received NHAART as the initial treatment had a higher total treatment cost (discounted and undiscounted) than a patient who had initially received PHAART. The difference of discounted cost between both at lifetime was 5%. Patients with initial NHAART however, also had higher QALYs and a longer survival rate than patients with initial PHAART. This was summarized in the cost-effectiveness plane in Figure 6.1 whereby initial NHAART was more costly but more effective than initial PHAART.

A trade-off therefore must be made between the additional health outcomes and the additional resources that must be committed to achieve those outcomes. In this study, initial PHAART, with CER of £7,379/LY and £10,253/QALY was considered as cost-effective compared to an initial treatment with NHAART based on the UK NICE's implied cost-effectiveness threshold of £20,000 - £30,000/QALY (Devlin and Parkin, 2004). These conclusions were robust against the uncertainty of estimates in quality of life, outpatient cost, and salvage treatment efficacy but was mildly sensitive to the first line initial treatment efficacy. However, as was reflected in the cost-effectiveness acceptability curve, it should be noted that the higher resource threshold that we would be able to commit (willingness to pay) or the more emphasis we place on the quality of life of patients, the higher probability that NHAART is the preferred choice for initial treatment.

There were no other studies that compared a ritonavir booster lopinavir regimen with an efavirenz based regimen as in this study. However, Caro (2001) have previously compared initial PHAART with initial NHAART regimen (Caro et al., 2001). The initial PHAART was based on indinavir as the protease inhibitor agent in the regimen, and efavirenz was the non nucleoside reverse transcriptase inhibitor agent in the NHAART regimen. Caro (2001) however, found that NHAART as an initial regimen was less costly than its PHAART counterpart, and also had a better survival rate that translated into a more cost-effective solution than initial PHAART.

The difference could be attributed to several factors. First of all, the cost of PHAART as an initial regimen in Caro (2001) was approximately 40% higher than NHAART whereas in the present study it was negligible. Secondly, in Caro (2001), the second and third line regimens were assumed to be the same for both PHAART and NHAART (ritonavir boosted saquinavir + 2 NRTI). Recent evidence in the resistance mechanisms of HIV led guidelines to emphasize switching treatments to at least two active drugs (Gazzard et al., 2006).

Different regimens would lead to different subsequent regimens and this was reflected in the present study model especially in the group that received initial NHAART. In this group, the third line regimen consists of a protease inhibitor and non nucleoside reverse transcriptase inhibitor class agent. The data on treatment for experienced patients was sparse especially on patients with initial NHAART. However, due to higher risks of cross resistance for NNRTI (Bangsberg et al., 2006) compared to PI, salvage treatment for NNRTI usually is in combination with a PI.

This study also had used efficacy estimates in experienced patients for model input of third line regimen rather than conditional estimates as in Caro (2001).

The cost-effectiveness analysis model above highlights two different conclusions. First of all, initial PHAART was more cost-effective in the long term care of HIV patients if the payer only cared about patient's survival as a health outcome measurement. Secondly, when health is defined holistically to include measurement of quality of life and this is given more emphasis by decision-makers by allowing a higher threshold, NHAART was more cost-effective as initial PHAART. This could be a better conclusion as reduced quality of life would adversely affect patient's adherence.

There are some limitations of the model which include: estimate of time to failure for salvage treatment; estimate of acute cost and quality of life; and the limitation of three regimens for patient in a lifetime. In addition, there is a possibility of cost underestimation due to exclusion of cost toxicity.

SUMMARY

- Initial treatment with NHAART was only less costly in the first three years than PHAART.
- NHAART had better survival rate than PHAART.
- PHAART less costly in the long term and had worst QALYs.
- PHAART more cost-effective than NHAART as initial regimen for gained survival and QALYs, but NHAART as an initial regimen was more cost-effective if the higher cost-effectiveness threshold with regards to QALYs was considered.
- The present model could be improved further in the future by including the cost of toxicity and acute care.

Chapter 7

General Discussion

Treatment of HIV infection has evolved immensely since 1996, from a single antiretroviral agent to a cocktail of at least three combinations of antiretroviral drugs from different pharmacological classes. These regimens which were called Highly Active Antiretroviral Treatment (HAART) have been attributed to the decrease in AIDS related death and morbidity.

Advances made across the discipline have increased the understanding of HAART's effect on total health and viral fitness. Although HAART has effectively suppressed the HIV virus, the multiple combinations of drugs have also brought forth problems with toxicity which consequently compromise patient quality of life. It has therefore been widely recognized that the health outcome of HAART needs to encompass the surrogate markers improvement, increase survival, reduce morbidity and improve quality of life (Forum for Collaborative HIV Research, 1999b).

The choice of initial combination from the array of antiretroviral agents available have been a primary focus in clinical research, especially the third drug, due to their significant but also varying degrees of viral suppression rates, treatment failure rates, viral resistance, and toxicity profiles. The choice became more important with evidence of increasing viral resistance rates in treatment experienced patients (Cane et al., 2005). Drugs from NNRTI groups were found to have higher resistance rates than PI. This was attributed to its vulnerability to cross resistance not only from previous exposure of the same class, but also from NRTI exposure.

Crucially, the initial regimen combination choice is an important clinical decision as it limits choice of subsequent combinations of HAART in treatment experienced patients. This issue has become even more important now that the disease itself has transformed into a chronic disease which translates into an increased need for an effective salvage regimen.

As the salvage treatment itself is more expensive, toxic and less effective than the first line regimen, there is an urgent need to understand the long term effects of initial regimens on patient outcomes. Unfortunately, although significant advancements have been made in understanding the impact of HAART combinations in HIV patients clinical outcomes, impacts on humanistic outcomes are still under-researched (refer Chapter 1).

Much of the preference based humanistic outcomes research in HIV has focused on the effect of patients' HIV stage and surrogate markers on the quality of life of patients (Delate and Coons, 2001, Mathews and May, 2007, Bayoumi and Redelmeier, 1999). Quality of life was found to deteriorate with increasing disease severity in these studies which could possibly be attributed to the effects of HAART. These relationships however were not explored in this study which was rather unfortunate since studies carried out using a psychometric quality of life instrument, the MOS-HIV, demonstrated that compared to NHAART, PHAART negatively affects patient quality of life even with a similar immunologic and virologic response (Fumaz et al., 2002). Whether these results will be replicated in preference based quality of life measurement remains unknown.

The high cost associated with HIV management, particularly antiretroviral drugs has received immense attention from policy makers, health authorities and physicians alike due to a realization of the scarcity of resources at hand. These resources, which could be used to fund other services, carry an opportunity cost that needs to be carefully justified.

Past studies demonstrated that antiretroviral drugs not only directly affect total patient care cost due to increased medications cost, but also indirectly due to a reduction in inpatient cost while at the same time increasing the outpatient cost

(Chen et al., 2006, Gebo et al., 1999, Bozzette et al., 2001). Unfortunately, these studies did not investigate the effect of different HAART combinations on the cost of patient care; especially in the long term, which could have been possible by considering the cascading effect of prior regimens on resistance, and toxicity. The results however underlined the importance of HAART as a predictor of patient's total care cost.

The results of different combinations of HAART effects on cost results, if available however, could not be taken as justification per se for treatment choices. The cost also needs to be balanced with patients' clinical and humanistic outcomes before arriving at a rational decision.

Rational decision-making can be analyzed within an economic framework. Addressing an issue from an economic perspective is simply trying to explicitly and systematically evaluate the choices in hand and determine the right balance of their cost and benefit. One way to have the right economic balance is by aiming for benefit maximization. This is achieved through the application of economic evaluation tools e.g. cost-effectiveness analysis and cost utility analysis.

However, in order for an economic evaluation to provide a sound conclusion, it requires quality data on costs and benefits of the choice at hand (Donaldson et al., 2002). In the absence of long term clinical trials or data on these outcomes, it was imperative for this study to investigate the effects or benefits of initial regimens on patient's outpatient costs and quality of life.

In order to achieve this aim, this study began with a longitudinal analysis of cost and quality of life in patients receiving outpatient care in the UK. As this study only had short time horizon, a Markov model was developed in later part of the study to estimate the long term horizon of patients cost, quality of life and survival outcomes.

IMPLICATIONS OF THE STUDY

The present study's contribution to the body of knowledge and its implications could be broadly summarized into two parts - outcome results and methodological.

Implications from Outcome Results

Study I: Resource Utilization and Cost Analysis

In order to investigate the effects of different initial regimens on costs, study I has analyzed the component cost of outpatient care over ten years. This study was therefore the first to look at the longitudinal effect of different initial regimens combinations on HIV patients' cost. The total outpatient cost itself was made up of the cost of procedures, outpatient clinic visits, laboratory tests, and imaging. All these costs were collected using a bottom-up analysis.

The statistical model of outpatient cost are of value to decision makers and physicians alike, who would like to control the factors and formulate policy that could both affect patients' outcomes.

The overall unadjusted mean outpatient monthly costs was estimated to be £237.59 (±152.32) with laboratory and clinic visits making up almost half of the cost each between them. This estimate was comparable to previous studies that had estimated the monthly outpatient cost to be between £161.31 and £315.95 (Gebo et al., 1999, Flori and le Vaillant, 2004). Temporal analysis of the component cost showed that the laboratory cost increased with time whilst clinic visit costs decreased. The trend replicated observations in Flori (2004) that saw outpatient cost decreasing from £241.39 in 1995 to £184.14 in 2000.

This trend could be attributed to manifestations of patient HIV progression towards a more severe HIV stage whereby more resources were used for diagnostic purposes. This was supported by the multilevel model of change findings that patients at the lowest immunity level with CD4+ stratum (<200 cells/mm^3) were estimated to have an 8.6% higher monthly cost than patients in the highest stratum (>500 cells/mm^3) which could be explained by the increased severity of HIV with reduction of immune cells. The findings that HIV symptomatic patients incurred 15% more outpatients costs than asymptomatic patients confirmed this suspicion. This reiterates the need for effective treatments in patients to alleviate their symptoms and improve their immune system.

The adjusted mean monthly cost of outpatient care from multilevel model of change was estimated to be £192.10. Initial regimen was confirmed to be a significant predictor with patients who received an initial NHAART regimen having a 1.1% average difference over time of monthly cost more than patients receiving PHAART as an initial treatment. The regimen that the patient was currently receiving when measured, surprisingly did not influence monthly cost. The findings confirmed the study hypothesis that different initial regimens have a different effect on costs; although it was expected that initial PHAART would incur more outpatient cost due to a higher incidence of toxicity associated with it (Barreiro et al., 2002a). This could warrant future study that investigating this effect.

Another explanatory variable that influenced monthly cost was nationality whereby British nationals were estimated to incur 21.3% less average cost compared to non British. Though the underlying mechanism of the difference still needs further investigation, the effect warranted clinic funding to be linked to migrant's distribution. The observation here could justify an increase of funding to clinics with high non

British nationals. This is especially so as migration was responsible for two thirds of the increase in the UK population in 2005 (Migration Watch UK, 2005). This figure nevertheless is set to increase with the expansion of European Union membership to include Eastern Europe.

Study II: Quality of Life of Patients with HIV

In this part of the study, the objective was to assess the impact of initial regimens on patients' quality of life. This study was therefore the first to examine the longitudinal effect of different initial regimen combinations on HIV patients' quality of life. Patient quality of life was assessed using Health Utility Index Mark 3 (HUI3) at three month intervals over a period of six months. Their quality of were initially analyzed at each cross section time using multivariate regression analysis. It was demonstrated that different variables had different roles in predicting HRQoL at different cross section times. This proved the inadequacy of cross sectional methods to assess the effect of time varying predictors and utilize the information that could be gained from repeated measurement study. Hence data was analyzed longitudinally using a multilevel model of change.

For the primary study objective, the baseline HRQoL score was found to be significantly predicted by initial treatment regimens with NHAART having a higher HRQoL followed by PHAART. Non HAART patients had a quality of life as poor as those patients not receiving any treatment. The effect seen was as expected, due to a higher treatment limitation toxicity report associated with PHAART (Bartlett and del Rio, 2001). Hence, if looking at improving patient's quality of life alone, NHAART would be a better choice for initial regimens.

There was no significant change over time in patients' quality of life suggesting that patient' formed preferences from their early HAART exposure experience. The findings however should be cautioned for long term generalization due to the short follow up of only 24 weeks.

It should also be noted that other observations in psychometric studies using MOS-HIV show that the HRQoL of patients receiving protease inhibitors remains unchanged until 96 weeks (Low-Beer et al., 2000).

Another significant predictor for baseline HRQoL was employment, whereby employed patients enjoyed better HRQoL than unemployed. This could suggest that employed patients enjoy a better quality of life than those unemployed. In fact, previous study found that unemployment is closely related to depression and social isolation (Feather, 1990). The availability of social workers that are responsible for patient social welfare in HIV clinics is therefore a step in the right direction to improve patients overall HRQoL.

This finding however could simply be due to the fact that sick people with the worst quality of life are unable to work. For this reason, treatment that could improve or preserve patients HRQoL would surely assist patients in finding and or keeping employment.

The decline in the rate of QoL over time was determined by HIV clinical stage whereby symptomatic patients' HRQoL declined faster than asymptomatic. Again, this is the reflection of disease progression towards a more severe HIV stage and underlines the need for an effective treatment that alleviates the symptoms.

Various factors affected both outcomes, with initial regimens found to be a significant predictor of both outcomes. Patient's disease progression which was characterized by surrogate markers significantly predicts cost but not quality of life.

Quality of life was however influenced by HIV stage. These observations highlight the importance of physical examination or outpatient consultation in monitoring patients' HRQoL and caution the over reliance on surrogate markers in patient health outcome monitoring.

The estimates of HRQoL and monthly outpatient cost in Study I and II would benefit health economists that seek to evaluate future HIV treatment with a more precise adjustment of the parameters.

Study III: Development of HIV Markov Chain Monte Carlo (MCMC)

Study III described the development stages involved in building an HIV progression model to explore the long term outcomes of initial regimens.

A Markov Chain Monte Carlo (MCMC) was developed using Treeage Pro 2007 to simulate HIV progression for 10,000 randomly drawn hypothetical patients. The patients were considered to be symptomatic with a randomly drawn viral load, age, and CD4 count.

The study began with treatment naïve patients in chronic states that had been initiated with HAART regimens. Their health regression or progression into acute ADE or death would follow at each cycle depending on their treatment outcomes and surrogate markers. The main difference between this model and other past models (Richter et al., 2002, Simpson et al., 2004, Caro et al., 2001) was that the present model took into account the dependence of salvage regimen combinations on the initial regimens and also it did not assume that patients would stop taking failing salvage treatments. In addition, the choice of drug combination and efficacy estimates were also updated in the model to reflect recent changes in the present body of knowledge.

The model was validated with patients who received no treatment and had demonstrated adequate internal consistency and convergence validity in comparison with survival models seen in past studies (Richter et al., 2002). This would allow the model to be applied in real clinical settings with reliable outcomes.

Study IV: Lifetime cost-effectiveness and cost utility analysis

The model in study III was used to explore long term outcomes of patients based on observations made in study I and II. It was found that initial treatment with NHAART using combinations of efavirenz, emcitrabine and tenofovir was only less costly in the first five years than PHAART that used combinations of ritonavir boosted lopinavir, lamivudine and zidovudine. Patients who received initial regimens of NHAART however had better survival rate and more QALYs than PHAART.

The economic evaluation analysis using hypothetical patients was the first study to compare the current guideline recommendations in first line HAART regimens i.e. ritonavir boosted lopinavir vs efavirenz that was based on the efficacy reported in a few short term and small clinical trials. Although physicians in the UK did show preference for efavirenz based regimens (Gazzard et al., 2006), this was based on their perceived toxicity of protease inhibitor rather than conclusive evidence on the cost and benefit of both choices. In the absence of long term large randomized clinical trials, economic evaluation through the use of Markov Chain Monte Carlo simulation model provided invaluable insight into the long term outcome comparison of these regimens.

The incremental cost-effectiveness ratio analysis of NHAART combination compared to PHAART as initial regimens was estimated to be £15,923/LY and £8,871/QALY gained. This was higher than ICER of £4,073/LY between HAART

combination reported in Simpson (2004). This could be attributed to the short survival gained of only 0.74 years with NHAART compared to Simpson (2004) that had 25 years survival gained. The survival estimate difference in this study however was more plausible as the hazard ratio of AIDS or death for patients with initial PHAART was estimated to be 1.45 compared to NHAART in a recent US and European cohort (The Antiretroviral Therapy Cohort Collaboration, 2006).

The study had found that NHAART with initial regimen based on efavirenz to be more costly with a slight gained in survival than initial regimen with PHAART. This results in concluding PHAART as more cost-effective than NHAART when looking at survival alone.

However the choice was not as clear cut when quality of life of patients is taken into considerations. Although, in this cost utility analysis initial PHAART was still cost-effective compared to NHAART, it loses its efficiency at the higher cost-effectiveness threshold i.e. beyond £27,500. Beyond this point, NHAART was more cost-effective as an initial regimen than PHAART. This threshold is well within the implied NICE ICER threshold of £20,000 to £30,000/QALY (Devlin and Parkin, 2004). In other words, the more the payer is willing to pay for an increase in quality adjusted life, the more likely NHAART will be the optimal choice.

As with any analytical tool, this conclusion only serves as an aid to decision makers. The decision to choose NHAART at a higher threshold value would still incur increased resources over the benefits. It is therefore up to the decision maker to assess how much emphasis should be given to the quality of life of patients.

However, in view of the importance of patient's quality of life as seen in Study II and its relationship to treatment adherence (Penedo et al., 2003), NHAART with a

combination of efavirenz is recommended as a more efficient choice for initial HAART regimen combinations.

Methodological Implications

Missing Data Handling: Multiple Imputation

Missing data handling mechanisms have not been described in previous studies except for the use of 'hot deck' imputation in Bozzette et al (2001). The worst assumption would be that other studies had used the statistical software default technique of handling missing data i.e. complete case analysis, which is inefficient as it excludes potentially informative data and is vulnerable to bias if the missing data systematically varies from the complete data (Briggs et al., 2003). Hot deck refers to imputation of missing values in incomplete records from similar but complete records in the same dataset. Although this technique is more efficient than complete case analysis, it does not reflect the additional uncertainty due to imputing for missing data (Allison, 2001).

This could be overcome through multiple imputations that take account of the variance of several imputation values into analysis. The detailed application of this technique in analysis of cost and HRQoL in HIV patients could improve missing data handling in future analysis of data in the field.

Longitudinal Multilevel Model of Change Application in Cost and HRQoL Analysis of HIV Patients

There are generally three requirements for establishing causality (Frees, 2004): establishment of significant relationship; association must not be due to an omitted variable; and the 'causal' variable must precede the other variable in time'. This study applied the longitudinal multilevel model (MLM) of change in the analysis of cost and preference based HRQoL in HIV patients. Through using longitudinal data collection, this study naturally met the third *ceteris paribus* requirement. The advantage of longitudinal analysis over pooled cross sectional analysis data as applied in Yazdanpanah et al (2002) and Flori and Valiant (2004) is that it allows for better control of individual heterogeneity by specifying the subject specific parameter in the model. This individual uniqueness is only accounted as unobserved effect error term in cross sectional model which could lead to heterogeneity bias (Wooldridge, 1999). As this subject specific effect accounts for a large portion of variation in many datasets, accounting for this effect results the in reduction of mean square error and increases efficiency of parameter estimators (Frees, 2004).

Longitudinal data analysis was used in cost analysis in Beck et al (1998), Gebo et al (1999), Bozzette et al (2001) and Chen et al (2006). What set this study apart from those was that this study a applied multilevel model (MLM) of change, the analytic technique rather than logistic regression (Beck et al., 1998b), univariate regression (Bozzette et al., 2001), generalized estimation equation (Gebo et al., 1999) and analysis of variance (Chen et al., 2006). The use of this method over these other analytical techniques was statistically justified following the observation of high intraclass correlations (ICC) of more than 0.4 units between measurements (Singer and Willett, 2003). This would violate the normal residual distribution assumption in other classic techniques whereas it is well accommodated for in the MLM technique. A comparison between results from cross sectional analysis and MLM was also

made in Study II, and the different conclusions between the two methods imply the effect of additional information obtained in repeated measurement on the model fit.

MLM also has the advantage over other previously applied methods of easily accommodating the unbalanced panel data, the result of varying follow up length between measurements (Diggle et al., 1996). This is especially important in longitudinal cohort studies such as this that have patients with varied resource utilization rates and questionnaire return rates.

The transparent detailed description of MLM application in the analysis of change in cost and HRQoL would allow wider application of this technique in this field. In addition, the technique application could be further refined in future studies including a more detailed analysis of non linearity and covariance structure which could not be achieved in this study due to STATA Intercooler 9.0 limitations. The quality of life of patients for example, was found to have a non linear relationship with independent variables. However, due to limitation of the statistical software in handling non linear multilevel models, only a limited power transformation was applied to the HRQoL score prior to analysis.

LIMITATIONS OF THE STUDY

Small sample size

This study was an observational study with no control on intervention allocation or randomization. This resulted in an insufficient and imbalanced sample size of patients with PHAART (n=25) compared to NHAART (n=69) due to a clear preference for NHAART by physicians in the study setting.

Furthermore, although the study initially intended to compare the specific combination of individual drugs, the regimens received by patients were highly varied and results in very small number of patients in each group. Therefore, the combination was compared in group of pharmacological class instead.

Other factors that influenced the size were a consequence of reliance on members of clinic for patient recruitment due to the strict privacy and sensitivity policy. Although physicians showed interest in the study, other members of the health care team were a bit reluctant due to the work load and space restriction in the clinics.

Missing information

As the data collection for resource utilization, demographic characteristics and clinical observations was primarily sourced from patient records, the amount of information collected was highly dependent on the quality of the medical records. Unfortunately, not all records were legible and poor record keeping further contributed to missing information.

In addition, due to the highly sensitive nature of the disease, a very strong data protection policy was employed throughout the clinic. No direct correspondence was allowed (limiting investigator control of subjects) to remind patients for questionnaire completion. This led to less control of patients' follow up questionnaire completion.

Some patients arrived in the clinic emotionally stressed and highly agitated, and therefore found in person follow up reminders and the questionnaire itself as a nuisance. In fact, the researcher was, on a few occasions, verbally harassed. These factors consequently lead to data missing for some information.

Absence of acute measurement

The data protection policy enforced in clinic restricts movement of patient records to other parts within the hospital for data extraction. In the case of other disease patients, records are allowed to be sent to another hospital upon request which was usually the case when acute inpatient care was in another hospital. The restriction placed on patient record movements lead to lack of acute care data in patient records which consequently limited the present study to chronic care only.

Absence of toxicity and adherence information

As both PHAART and NHAART have different toxicity profile, there are highly likely to differ in resources required for treatment of the adverse effects. Unfortunately the medication record of non antiretroviral treatment for patients was incomplete. This forced the study to exclude this effect.

RECOMMENDATIONS AND FUTURE WORK

As in any other studies, the results sometimes generate more questions than they answer. It is therefore the responsibility of this section to highlight the possibilities that could be explored with future work in this exciting field.

The Markov Chain Monte Carlo model of HIV progression could be used in the future to model or compare different treatment strategies. More input on the effect of salvage treatment and acute care cost and quality of life however is required to improve the model's prediction. The present chronic monthly cost and quality of life statistical model could be useful for future studies. It would be of interest, however, to explore and compare this model within acute settings.

The findings of higher outpatients care costs for patients with initial NHAART compared to patients receiving initial PHAART could not be explained by the present data. The explanation could lie in effect of non HIV stage modifying symptoms and adverse drug reactions that were unfortunately unavailable in this study. This question could be explored in a future study that could collect more thorough clinical data.

In addition, due to the study design limitations, patient's quality of life was not assessed at treatment initiation but only at the cross section assessed time. A more informative longitudinal method that could assess the impact of treatment would be to collect the HRQoL routinely from the time the patient initiates or switches treatment.

In conclusion, it is believed that the work presented in this thesis has made a valuable contribution to the existing body of knowledge in this area. Specifically, the work has enriched understanding of the impact of different initial regimens on the patient's outcome. This will be beneficial to aid HIV treatment decision-making.

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PUBLICATIONS

ABSTRACTS

Salek, M. S., A. A. Shafie, et al. (2005). Can systematic assessment of patients' quality of life influence optimisation of HIV treatment? 34th European Symposium on Clinical Pharmacy, Amsterdam, European Society of Clinical Pharmacy.

Salek, M. S., A. A. Shafie, et al. (2005). The case for HRQoL assessment: key to successful HIV treatment. 34th European Symposium on Clinical Pharmacy, Amsterdam, European Society of Clinical Pharmacy.

Shafie, A. A., M. S. Salek, et al. (2005). Self assessed health-related quality of life among HIV patient in UK. ISPOR 8th Annual European Congress, Florence, ISPOR.

Shafie, A. A., M. S. Salek, et al. (2005). "Assessment of health related quality of life in patient with HIV: is it practical?" International Journal of Pharmacy Practice **13**(Supp). Commended Poster Award: poster presentation at the *British Pharmaceutical Conference*, 26 – 28 Sep 2005, Manchester, UK.

Shafie, A. A., M. S. Salek, et al. (2005). "Cross-cultural validity and reliability of Health Utility Index 3 in patients with HIV." Quality of Life Research **14**(9): 2153.

Salek, M. S., A. A. Shafie, et al. (2006). Routine HRQoL monitoring in patients with HIV. 13th Annual Conference of the International Society for Quality of Life Research. Lisbon, Portugal.

APPENDIX I:

ETHICAL APPROVAL LETTER

Canolfan Gwasanaethau Busnes
Business Services Centre

South East Wales Research Ethics Committees
Direct Line 02920 402309/402420

Our ref: SMKW/EL/jl/04/WSE03/71

24 September 2004

Dr Sam Salek,
Welsh School of Pharmacy,
Cardiff University
Redwood Building
King Edward VII Avenue
Cardiff, CF10 3XF

Dear Dr Salek

REC reference number: 04/WSE03/71 : Assessment of the treatment strategies and the factors influencing treatment decisions for HIV infection
Investigator: Dr Sam Salek, Welsh School of Pharmacy, Cardiff University

Thank you for your letter of the 20th September 2004, responding to the South East Wales Research Ethics Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the South East Wales Executive Sub-Committee held on 24th September 2004.

The Members present at the meeting were Miss S M K Williams (Chairman) and Dr B Patel (GP Member).

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

The favourable opinion applies to the following research site:

Site:	**Welsh School of Pharmacy, Centre for Socio Economic Research, Cardiff University, King Edward VII Avenue. CF10 3XF**
Principal Investigator:	**Dr Sam Salek**

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Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type: Application
Version: 16/08/2004
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Investigator CV
Version: Dr Sam Salek
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Protocol
Version: 2
Dated: 20th September 2004
Date Received: 20th September 2004

Document Type: Summary/Synopsis
Version: 2
Date Received: 20/09/2004

Document Type: Copy of Questionnaire
Version: HIV Clinical Decision Making Questionnaire
Dated: 20/09/2004
Date Received: 20/09/2004

Document Type: Copy of Questionnaire
Version: Healthy Utility Index Questionnaire
Dated: no version, undated

Document Type: Participant Information Sheet
Version: 2
Dated: 20/09/2004

South East Wales Research Ethics Committees
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Document Type: Participant Consent Form
Version: 2
Dated: 20/09/2004

Document Type: Consultant Physician Information Sheet
Version: 2 - HIV Clinical Decision Making
Dated: 20/09/2004

Document Type: Participant Consent Form
Version: 2 - HIV Clinical Decision Making
Dated: 20/09/2004

Management approval

The Committee noted your declaration (A6 of application form) that this is a study with no local investigators. The Committee agreed that this is a "no local investigator" study and site-specific assessment is not required for sites involved in the research. No information about the study needs to be submitted to Local Research Ethics Committees. However, you should arrange for all relevant host organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Notification of other bodies

We shall notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

South East Wales Research Ethics Committees
Direct Line 02920 402309/402420

REC reference number: 04/WSE03/71 - Please quote this number on all correspondence

Yours sincerely

Miss S M K Williams
Chairman Panel C
South East Wales Research Ethics Committees

Enclosures: Standard approval conditions [SL-AC2]

APPENDIX II:

Patient Information Sheet

Patient Information Sheet

Quality of Life Assessment in Patients

This information sheet has been designed to give you information about this study. If you have any further queries, please feel free to contact Dr Richard Evans or Dr Sam Salek (Phone at work: 02920876017).

Purpose of the Study

You are invited to participate in a research study designed to determine the changes of your quality of life after receiving prescribed treatment. The questionnaire used, namely the Health Utility Index 3 (HUI3) is the most suitable tool to monitor your quality of life. The result of this study will provide your doctor with better understanding of your functional ability and helps them in their clinical assessment. In addition, this will enhance future studies designed to assess the effects of drug treatment regimes used in your care.

Study Background

Drug treatment is an important part of multidisciplinary aspect of a treatment that aimed at achieving the best quality of life for patients. In spite of its effectiveness in the disease treatment, in some occasion, it may make some patients feel worse. Hence, it is essential for quality of life to be measured for the full treatment effect to be realized. The HUI3 questionnaire has been chosen as measuring tool because of its wide use and acceptability by people like you.

Your Participation

If you decide to participate in the study, you will be asked to complete the HUI3 questionnaire during your visit to out-patient clinic. This self-administered questionnaire will take about 10 minutes to complete. Three set of HUI3 questionnaires will be provided to you in this visit. You only have to complete one of

them during this visit. The other two questionnaires should be completed and send to us in the provided envelope, one at each subsequent visit. All information collected from your participation will be treated in the strictest confidence and be used only for the purpose of this study. This information will be destroyed at the end of the study. Your name will be kept confidential and will not be mentioned in any report or publication. For confidentiality purpose too, your participation in this study will not be informed to your GP unless you wish otherwise.

Informed Consent

Your doctor will further explain the details of the study and answer any questions which you may have. You will be asked to sign an informed consent stating that you understand the nature of the study and what is required from you in the study.

Participation in this study is voluntarily and will not affect your current or future treatment. You are free at any time to change your mind and withdraw from the study without needing to justify your decision, and this will not affect your care in any way.

Thank you for your co-operation.

APPENDIX III:

Informed Consent

INFORMED CONSENT DECLARATION

Quality of life assessment in patients receiving care

1. I, undersigned voluntarily, agree to take part in this study which I understand has been approved by an independent ethics committee.
2. I confirm that a full explanation of the purpose and nature of the study has been given to me and that I have read and understood the given 'information for volunteers' (Patient Information Sheet 20 September 2004 Version 2.0).
3. I have been given the opportunity to ask question on all aspects of the study and have understood the advice and information given as a result.
4. I agree to co-operate faithfully with the studying investigators with regard to my eligibility to participate in the study.
5. I also understand that failure to take part will no way prejudice my further treatment.
6. I consent to the investigators having access to the information in my records, with the understanding that any publication shall not reveal my name or any other personally identifying information.

Signature: ..... Date: .....

(Patient)

I confirm that I have explained the nature and purpose of the study to this volunteer. If, at any time during the course of this study, new information develops that may affect the volunteer's willingness to continue participation, a statement of this information will be provided to the patient.

Patient Name: (Block Capitals)

Signature: Date:

(Consultant Physician)

Witness: Date:

20 September 2004 Version 2.0

APPENDIX IV:

HIV Research Database Outline

Properties

AccessVersion:	08.50	AllowBuiltInToolbars:	True
AllowFullMenus:	True	AllowShortcutMenus:	True
AllowSpecialKeys:	True	AllowToolbarChanges:	True
ANSI Query Mode:	0	Auto Compact:	0
Build:	566	CollatingOrder:	General
ColumnLevelTracking:	True	DefaultPartner:	{guid {00000000-0000-0000-0000-000000000000}}
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ProjVer:	35	QueryTimeout:	60
RecordsAffected:	0	ReorderTables:	F
Replicable:	T	ReplicableBool:	True
ReplicaID:	{guid {6329364F-CFB0-4236-AE63-CEF1C95FF579}}	ReplicaPriority:	81
Row Limit:	10000	Show Values in Indexed:	1
Show Values in Non-Indexed	1	Show Values in Remote:	0
Show Values in Server:	0	Show Values in Snapshot:	1
Show Values Limit:	1000	StartUpForm:	Form.Switchboard
StartUpShowDBWindow:	True	StartUpShowStatusBar:	True
Transactions:	True	Updatable:	True
Use Default Connection File:	0	Use Default Page Folder:	0
UseAppIconForFrmRpt:	False	Version:	4.0

User Permissions

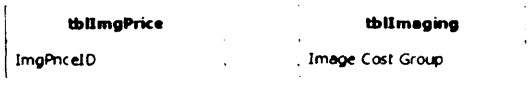
admin

Group Permissions

Admins
Users

Relationships

tblImgPricetblImaging



Attributes:	Not Enforced
RelationshipType:	One-To-Many

tblRiskFactortblPatient

Attributes:	Not Enforced
RelationshipType:	One-To-Many

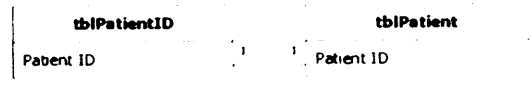
tblLaboratorytblLabResult

Attributes:	Not Enforced
RelationshipType:	One-To-Many

tblDrugtblMedication

Attributes:	Not Enforced
RelationshipType:	One-To-Many

tblPatientIDtblPatient

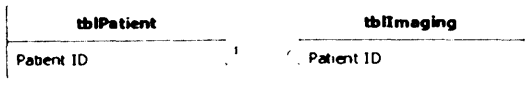


Attributes:	Unique, Enforced, Cascade Updates
RelationshipType:	One-To-One

tblPatienttblClinicVisit

Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

tblPatienttblImaging



Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

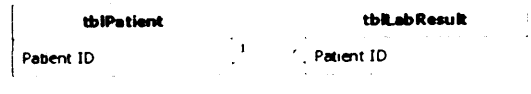
tblPatienttblImmunoStatus

Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

tblPatienttblInpatient

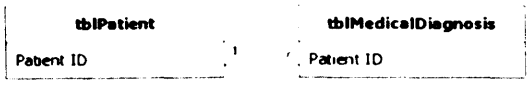
Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

tblPatienttblLabResult



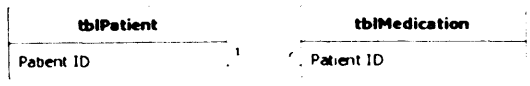
Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

tblPatienttblMedicalDiagnosis



Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

tblPatienttblMedication



Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

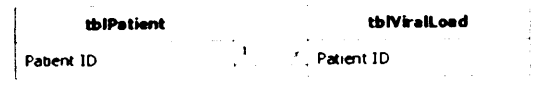
tblPatienttblProcedure

Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

tblPatienttblQualityOfLife

Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

tblPatienttblViralLoad



Attributes:	Enforced, Cascade Updates
RelationshipType:	One-To-Many

APPENDIX V:

Demographic Enquiry Form

In order to monitor the impact of the treatment, it is necessary to collect information from patients on the key characteristics, which relate to equality and diversity in treatment. This form is only used to assist us in this research statistic and WILL NOT be taken into consideration for your treatment. The information collected will be used under the term of the Data Protection Act 1998.

Patient ID: _____

Area Postcode: _____

NATIONALITY

☐ British

☐ Other
Please specify

ETHNICITY

You are asked to classify yourself in the category, which you feel most nearly describes your origin. If none of the specific groups are suitable please mark the relevant 'Other' and specify your ethnicity.

I would categorise my ethnic origin as

☐ **ASIAN OR ASIAN BRITISH**

☐ **BLACK OR BLACK BRITISH**

☐ **MIXED**

☐ **CHINESE**

☐ **WHITE**

☐ **OTHER ETHNIC BACKGROUND**
Please specify _____

EMPLOYMENT

☐ Employed

☐ Unemployed

APPENDIX VI:

Health Utility Index Mark 3 (HUI3)

HEALTH UTILITY INDEX (HUI)

Patient ID Number: _____ Date: _____

The next set of questions asks about your day-to-day health. The questions are not about illnesses like colds that affect people for short periods of time. They are concerned with a person's usual abilities. You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone.

VISION

		YES	NO
1.	**Are you <u>usually</u> able to see well enough to read ordinary newsprint <u>without</u> glasses or contact lenses?** -------	☐	☐

If you ticked YES, please go to question 4

If you DON'T KNOW, or REFUSED, this questionnaire will end here

2.	**Are you <u>usually</u> able to see well enough to read ordinary newsprint <u>with</u> glasses or contact lenses?** -------	☐	☐

If you ticked YES, please go to question 4

3.	**Are you able to see at all?** -------	☐	☐

If you ticked NO, please go to question 6

If you DON'T KNOW, or REFUSED, please go to question 6

4.	**Are you able to see well enough to recognize a friend on the other side of the street <u>without</u> glasses or contact lenses?** -------	☐	☐

If you ticked YES, please go to question 6

If you DON'T KNOW, or REFUSED, please go to question 6

5. **Are you <u>usually</u> able to see well enough to recognize a friend on the other side of the street <u>with</u> glasses or contact lenses?** ------- ☐ ☐

HEARING

		YES	NO
6.	**Are you <u>usually</u> able to hear what is said in a group conversation with at least 3 other people <u>without</u> a hearing aid?** -------	☐	☐

If you ticked YES, please go to question 10

If you DON'T KNOW, or REFUSED, please go to question 10

7.	**Are you <u>usually</u> able to hear what is said in a group conversation with at least 3 other people <u>with</u> a hearing aid?** -------	☐	☐

If you ticked YES, please go to question 8

7.A.	**Are you able to hear at all?** -------	☐	☐

If you ticked NO, please go to question 10

If you DON'T KNOW, or REFUSED, please go to question 10

8.	**Are you <u>usually</u> able to hear what is said in a conversation with one other person in a quiet room <u>without</u> a hearing aid?** -------	☐	☐

If you ticked YES, please go to question 10

If you REFUSED, please go to question 10

9.	**Are you <u>usually</u> able to hear what is said in a conversation with one other person in a quiet room <u>with</u> a hearing aid?** -------	☐	☐

SPEECH

		YES	NO
10. **Are you <u>usually</u> able to be understood <u>completely</u> when speaking with strangers in your own language?**	-------	☐	☐

If you ticked YES, please go to question 14

If you REFUSED, please go to question 14

11. **Are you able to be understood <u>partially</u> when speaking with strangers?**	-------	☐	☐
12. **Are you able to be understood <u>completely</u> when speaking with those who know you well?**	-------	☐	☐

If you ticked YES, please go to question 14

If you REFUSED, please go to question 14

13. **Are you able to be understood <u>partially</u> when speaking with those who know you well?**	-------	☐	☐

GETTING AROUND

		YES	NO
14. **Are you <u>usually</u> able to walk around the neighbourhood <u>without</u> difficulty and <u>without</u> mechanical support such as braces, a cane or crutches?**	-------	☐	☐

If you ticked YES, please go to question 21

If you DON'T KNOW, or REFUSED, please go to question 21

15. **Are you able to walk at all?**	-------	☐	☐

If you ticked NO, please go to question 18

If you DON'T KNOW, or REFUSED please go to question 18

16. **Do you require mechanical support such as braces, a cane or crutches to be able to walk around the neighbourhood?** ------- ☐ ☐

17. **Do you require the help of another person to be able to walk?** ------- ☐ ☐

18. **Do you require a wheelchair to get around?** ------- ☐ ☐

If you ticked NO, please go to question 21

If you DON'T KNOW, or REFUSED, please go to question 21

19. **How often do you use a wheelchair?**

	Please Tick One Only	Official Use Only
Always		
Often		
Sometimes		
Never		

20. **Do you need the help of another person to get around in the wheelchair?** ------- ☐ ☐

HANDS AND FINGERS

	YES	NO
21. **Are you <u>usually</u> able to grasp and handle small objects such as a pencil or scissors?** -------	☐	☐

If you ticked YES, please go to question 25

If you DON'T KNOW, or REFUSED, please go to question 25

22. **Do you require the help of another person because of limitations in the use of hands or fingers?** ------- ☐ ☐

If you ticked NO, please go to question 24

If you DON'T KNOW, or REFUSED, please go to question 24

16. **Do you require mechanical support such as braces, a cane or crutches to be able to walk around the neighbourhood?** ------- ☐ ☐

17. **Do you require the help of another person to be able to walk?** ------- ☐ ☐

18. **Do you require a wheelchair to get around?** ------- ☐ ☐

If you ticked NO, please go to question 21

If you DON'T KNOW, or REFUSED, please go to question 21

19. **How often do you use a wheelchair?**

	Please Tick One Only	Official Use Only
Always		
Often		
Sometimes		
Never		

20. **Do you need the help of another person to get around in the wheelchair?** ------- ☐ ☐

HANDS AND FINGERS

YES NO

21. **Are you <u>usually</u> able to grasp and handle small objects such as a pencil or scissors?** ------- ☐ ☐

If you ticked YES, please go to question 25

If you DON'T KNOW, or REFUSED, please go to question 25

22. **Do you require the help of another person because of limitations in the use of hands or fingers?** ------- ☐ ☐

If you ticked NO, please go to question 24

If you DON'T KNOW, or REFUSED, please go to question 24

23. **Do you require the help of another person with:**

	Please Tick One Only	Official Use Only
some tasks?		
most tasks?		
almost all tasks?		
all tasks?		

	YES	NO
24. **Do you require special equipment, for example, devices to assist in dressing, because of limitations in the use of hands or fingers?** -------	☐	☐

FEELINGS

25. **Would you describe yourself as being usually:**

	Please Tick One Only	Official Use Only
happy and interested in life?		
somewhat happy?		
somewhat unhappy?		
unhappy with little interest in life?		
so unhappy that life is not worthwhile?		

MEMORY

26. **How would you describe your usual ability to remember things?**

	Please Tick One Only	Official Use Only
Able to remember most things		
Somewhat forgetful		
Very forgetful		
Unable to remember anything at all		

THINKING

27. **How would you describe your <u>usual</u> ability to think and solve day-to-day problems?**

	Please Tick One Only	Official Use Only
Able to think clearly and solve problems		
Having a little difficulty		
Having some difficulty		
Having a great deal of difficulty		
Unable to think or solve problems		

PAIN AND DISCOMFORT

	YES	NO
28. **Do you <u>usually</u> free of pain or discomfort?** -------	☐	☐

If you ticked YES, this questionnaire will end here

If you DON'T KNOW, or REFUSED, this questionnaire will end here

29. **How would you describe the <u>usual</u> intensity of your pain or discomfort?**

	Please Tick One Only	Official Use Only
Mild		
Moderate		
Severe		

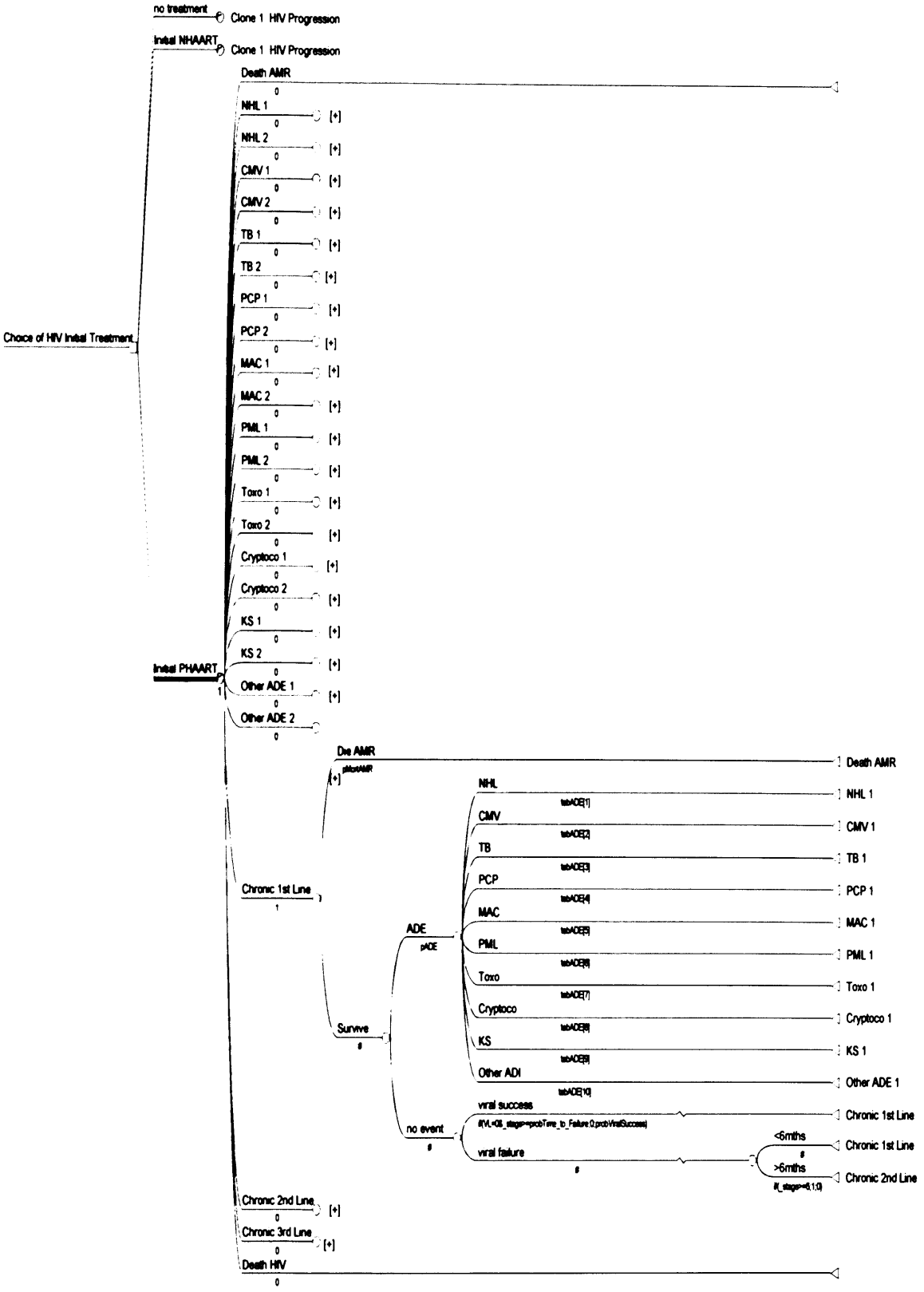
30. **How many activities does your pain or discomfort prevent?**

	Please Tick One Only	Official Use Only
None		
A few		
Some		
Most		

Thank you for your participation

APPENDIX VII:

Markov Monte Carlo HIV Model Outline


Choice of HIV Initial Treatment
no treatment
Clone 1 HIV Progression
Initial NHAART
Clone 1 HIV Progression
Initial PHAART
Death AMR
NHL 1
NHL 2
CMV 1
CMV 2
TB 1
TB 2
PCP 1
PCP 2
MAC 1
MAC 2
PML 1
PML 2
Toxo 1
Toxo 2
Cryptoco 1
Cryptoco 2
KS 1
KS 2
Other ADE 1
Other ADE 2
Chronic 1st Line
Chronic 2nd Line
Chronic 3rd Line
Death HIV
Die AMR
Survive
ADE
pADE
NHL
CMV
TB
PCP
MAC
PML
Toxo
Cryptoco
KS
Other ADI
tabADE[1]
tabADE[2]
tabADE[3]
tabADE[4]
tabADE[5]
tabADE[6]
tabADE[7]
tabADE[8]
tabADE[9]
tabADE[10]
Death AMR
NHL 1
CMV 1
TB 1
PCP 1
MAC 1
PML 1
Toxo 1
Cryptoco 1
KS 1
Other ADE 1
no event
viral success
viral failure
Chronic 1st Line
<6mths
Chronic 1st Line
>6mths
Chronic 2nd Line

APPENDIX VIII:

Statistical Syntax for Multiple Imputation of Missing Data

STATA Syntax in ICE Module for Multiple Imputation of Cost and Quality of Life Data

ICE imputes missing values in *mainvarlist* by using switching regression, an iterative multivariable regression technique. ICE provides many options that could be used to specify the imputation model. Some of the main command used in the present syntax are:

`cmd` defines the regression commands to be used for each variable in *mainvarlist*, `eq` allows one to define customised prediction equations for any subset of variables in *mainvarlist*, `cycles(#)` determines the number of cycles of regression switching to be carried out, and `boot` invokes a bootstrap method for creating imputed values.

Syntax for Imputation of Missing Data in Cost Analysis (Study I):

```
ice loc1 loc2 criskfactor2 rf1 rf2 rf3 cemployment emp1 emp2 emp3 emp4 age
/*
*/sex1 sex2 nationality3 nat1 nat2 nat3 icat1 icat2 icat3 icat4 ccat1
ccat2 ccat3 ccat4 /*
*/vlcat vl1 vl2 cd4cat cd1 cd2 cd3 stage1 stage2 stage3 ethn1 ethn2 ethn3
ethn4 using imp, m(5) /*
*/passive(rf1:(criskfactor2==1) \rf2:(criskfactor2==2)
\rf3:(criskfactor2==3) /*
*/\emp1:(cemployment==1) \emp2:(cemployment==2) \emp3:(cemployment==3)
\emp4:(cemployment==4) /*
*/\nat1:(nationality3==1) \nat2:(nationality3==2) \nat3:(nationality3==3)
/*
*/\vl1:(vlcat==1) \vl2:(vlcat==2) \cd1:(cd4cat==1) \cd2:(cd4cat==2) /*
*/\cd3:(cd4cat==3)) sub(criskfactor2: rf1 rf2 rf3,cemployment:emp1 emp2
emp3 emp4,/*
*/nationality3: nat1 nat2 nat3,vlcat: vl1 vl2,cd4cat:cd1 cd2 cd3) /*
*/cmd(vlcat:ologit,cd4cat:ologit) /*
*/eq(vlcat: cd4cat stage1 stage2 stage3 criskfactor2,cd4cat: vlcat stage1
stage2 stage3 criskfactor2,/*
*/criskfactor2: loc2 ethn1 ethn2 ethn4) /*
*/boot(criskfactor2) replace
```

Syntax for Imputation of Missing Data in HRQoL Analysis (Study II):

```
ice vision hearing speech ambulation dexterity emotion cognition pain
avgofcd34 /*
*/avgofviralload riskfactor rf1 rf2 rf3 rf4 hivstage chivstage1 chivstage2
chivstage3 /*
*/british white /*
*/employment emp1 emp2 emp3 emp4 curreg creg1 creg2 creg3 creg4 /*
```

```
*/initreg iregl ireg2 ireg3 ireg4 location female age using imp, m(5) /*
*/passive(rfl:(riskfactor==1) \rf2:(riskfactor==2) \rf3:(riskfactor==3)
\rf4:(riskfactor==4) /*
*/\chivstagel:(hivstage==1) \chivstage2:(hivstage==2)
\chivstage3:(hivstage==3) /*
*/\empl:(employment==1) \emp2:(employment==2) \emp3:(employment==3)
\emp4:(employment==4) /*
*/\cregl:(curreg==1) \creg2:(curreg==2) \creg3:(curreg==3)
\creg4:(curreg==4) /*
*/\iregl:(initreg==1) \ireg2:(initreg==2) \ireg3:(initreg==3)
\ireg4:(initreg==4)) /*
*/sub(riskfactor:rfl rf2 rf3 rf4,hivstage:chivstagel chivstage2
chivstage3,/*
*/employment:empl emp2 emp3 emp4,curreg:cregl creg2 creg3 creg4,/*
*/initreg:iregl ireg2 ireg3 ireg4) /*
*/cmd(hivstage:ologit,vision:regress,hearing:regress,speech:regress,ambula
tion:regress,/*
*/dexterity:regress,emotion:regress,pain:regress)/*
*/eq(vision: hearing speech ambulation dexterity emotion cognition pain
avgofcd34 /*
*/avgofviralload chivstagel chivstage2 chivstage3 cregl creg2 creg3 creg4
age,/*
*/hearing: speech ambulation dexterity emotion cognition pain avgofcd34 /*
*/avgofviralload chivstagel chivstage2 chivstage3 cregl creg2 creg3 creg4
age,/*
*/speech: hearing ambulation dexterity emotion cognition pain avgofcd34 /*
*/avgofviralload chivstagel chivstage2 chivstage3 cregl creg2 creg3 creg4
age,/*
*/ambulation: hearing speech dexterity emotion cognition pain avgofcd34 /*
*/avgofviralload chivstagel chivstage2 chivstage3 cregl creg2 creg3 creg4
age,/*
*/emotion: hearing speech ambulation dexterity cognition pain avgofcd34 /*
*/avgofviralload chivstagel chivstage2 chivstage3 cregl creg2 creg3 creg4
age,/*
*/cognition: hearing speech ambulation dexterity emotion pain avgofcd34 /*
*/avgofviralload chivstagel chivstage2 chivstage3 cregl creg2 creg3 creg4
age,/*
*/pain: hearing speech ambulation dexterity emotion cognition avgofcd34 /*
*/avgofviralload chivstagel chivstage2 chivstage3 cregl creg2 creg3 creg4
age,/*
*/avgofcd34: avgofviralload chivstagel chivstage2 chivstage3 cregl creg2
creg3 creg4,/*
*/avgofviralload: avgofcd34 chivstagel chivstage2 chivstage3 cregl creg2
creg3 creg4,/*
*/hivstage: avgofcd34 avgofviralload cregl creg2 creg3 creg4 age,/*
*/employment: chivstagel chivstage2 chivstage3 british age /*
*/white location female,/*
*/british: chivstagel chivstage2 chivstage3 white location female /*
*/rfl rf2 rf3 rf4 empl emp2 emp3 emp4,/*
*/white: british chivstagel chivstage2 chivstage3 location rfl rf2 rf3 rf4
empl emp2 emp3 emp4 female,/*
*/curreg: avgofcd34 avgofviralload chivstagel chivstage2 chivstage3 iregl
ireg2 ireg3 ireg4,/*
*/initreg: avgofcd34 avgofviralload chivstagel chivstage2 chivstage3,/*
*/riskfactor: british chivstagel chivstage2 chivstage3 location /*
*/avgofcd34 empl emp2 emp3 emp4 female) /*
*/boot(avgofcd34 avgofviralload) /*
*/match(hearing emotion cognition pain avgofcd34 avgofviralload) replace
```