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A STUDY OF THE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON THE PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS OF HIV INFECTION.

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A thesis submitted for the degree of Doctor in Philosophy.

University of Dublin, Trinity College.

2000

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SUMMARY

The HIV pandemic has resulted in the most intense and as yet unparalleled effort devoted to antimicrobial drug development ever to be initiated in the developed world. The intensive drug research and development, compressed pre-clinical trials and expanded access programs have increased the number of therapeutic options. While the accelerated release of drugs is undoubtedly helpful, the attenuation of pre-licensing studies limits the availability of long term and rare adverse event data. Generation of such data is essential to guide clinicians in the optimal use of these drugs.

The rapid enlargement in the antiretroviral armamenterium and the primacy of drug therapy, in conjunction with the expansion of the criteria for initiation of antiretroviral therapy has resulted in increased expenditure on the management of HIV-infected individuals. Pharmacoeconomics is that branch of health economics that focuses on the costs and benefits associated with drug therapy particularly in high-cost areas. Highly active antiretroviral therapy (HAART) was adopted as standard of care in Ireland from mid-1996. Outpatient expenditure on HIV-related medication at St James's Hospital, Dublin doubled from approximately IR£0.5m in 1995 to IR£1m the following year. It was proposed that increased expenditure on HAART would be offset by decreased cost of treating opportunistic disease and reduced expenditure on inpatient care. However, testing this hypothesis was hampered by the dearth of observational cohort data and information on cost of health care for the HIV-infected cohort. The aim of this thesis was therefore to assess the impact of HAART on the pharmacoepidemiology and pharmacoeconomics of HIV infection in Ireland.

An observational cohort database was constructed to generate data detailing characteristics of the active cohort, morbidity, mortality and resource consumption. A substantive

improvement in surrogate marker data and a marked decrease in morbidity and mortality as evaluated by progression rate, incidence of AIDS defining illnesses and hospitalisation rate was observed over the study period. Increased numbers of new attendees combined with a decline in mortality has resulted in an almost doubling of the size of the active cohort. Furthermore, an overall increase in the proportion of participants who are female, have acquired HIV through heterosexual transmission and who were born outside of Ireland has been noted.

Use of HAART, although associated with unprecedented antiviral efficacy, is fraught with a number of difficulties including considerable toxicity profiles of some of the constituent antiretrovirals including the protease inhibitors. Following an extensive literature review, comparative profiles of the protease inhibitors were constructed. Furthermore, all patient-protease inhibitor exposures in the first three years of HAART therapy were included in a prospective drug toxicity surveillance study to characterise the tolerability profiles of these agents in an Irish clinic population. This study provides an important means of evaluating the profile and magnitude of adverse drug reactions in a cohort in which women, intravenous drug users and patients co-infected with hepatitis B and/or C are represented at higher proportions than in many of the clinical trial settings.

The introduction of HAART coincided with an overall decrease in aggregate expenditure on outpatient pharmacotherapy of four opportunistic infections examined in detail. However, despite a decrease in the incidence, specific opportunistic infections exhibited different patterns of expenditure on pharmacotherapy. Outpatient expenditure on drug therapy of MAC and CMV retinitis increased initially and then decreased, expenditure on candida decreased immediately whereas the cost of treating toxoplasmosis actually increased. This finding highlights the complexities inherent in pharmacoeconomic

evaluation of HIV disease, which is in fact a constellation of numerous specific clinical entities.

Methodology for the estimation of the cost of HIV healthcare was developed. A microcosting approach was taken to estimating the cost of inpatient care. This study identified an inverse relationship between CD4 cell count at baseline and the cost of inpatient care. HIV related admissions were associated with a higher cost than non-HIV related admissions. Furthermore this study revealed that ward costs, which are dependent on length of stay constitute the majority of admission costs for HIV-infected individuals regardless of diagnosis or immunological function. Estimation of the cost of care by the DRG casemix method, which is used to calculate a portion of prospective budgets for hospitals, grossly underestimated the actual cost of inpatient care.

Total expenditure on providing healthcare to our cohort doubled from almost IR£2 million in 1995 to approximately IR£4 million in 1998. This increase in expenditure occurred due to expansion in the size of the active cohort and also because of an increase in mean expenditure per active patient. The incremental increase in mean expenditure on antiretroviral therapy per active patient over the study period was IR£3,461. Meanwhile, the incremental increase in total cost of HIV-related health-care was only IR£1,869. The increases in expenditure noted coincided with a 79% decline in mortality rate per 100 active patients from 16.8 in 1995 to 3.5 in 1998.

These pharmacoeconomic evaluations generated interesting and useful data on the associated costs and benefits of HAART. However, the more far-reaching application of this work is that applying simplistic pharmacoeconomic methodologies in HIV disease may lead to erroneous conclusions.

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GLOSSARY

ABV	Abacavir
ACTG	AIDS Clinical Trials Group
ADR	Adverse drug reaction
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transferase
AMP	Amprenavir
AST	Aspartate transferase
AUC	Area under the concentration time curve
bd	Twice daily
CDC	Centre for Disease Control
C_{max}	Maximum Serum Concentration
CMI	Casemix index
CMV	Cytomegalovirus
CT	Computerised tomography
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DLV	Delavirdine
d-MAC	Disseminated *Mycobacterium avium c*omplex
DNA	Deoxyribonucleic acid
DRG	Diagnosis Related Group
EC_{90}	90% effective concentration
EFV	Efavirenz
FDA	Federal Drugs Administration
GGT	Gamma glutamyl transferase
HAART	Highly Active Antiretroviral Therapy
HIPE	Hospital In-Patient Enquiry
HIV	Human Immunodeficiency Virus
IDSA	Infectious Diseases Society of America
IDV	Indinavir
iv	Intravenously

LDH	Lactate dehydrogenase
MAC	*Mycobacterium avium* complex
MIMS	Medical Index of Medical Specialities
MRI	Magnetic resonance imaging
MTB	*Mycobacterium tuberculosis*
NFV	Nelfinavir
NVP	Nevirapine
od	Once daily
PCP	*Pneumocystis carinii* pneumonia
po	Orally
RNA	Ribonucleic acid
RTV	Ritonavir
SQV_{hgc}	Saquinavir (hard gel capsule)
SQV_{sgc}	Saquinavir (soft gel capsule)
TB	Tuberculosis
tds	Three times daily
ZDV	Zidovudine
1999*	Data for the first two quartiles only of 1999
1999^{proj}	Data from the first two quartiles of 1999 projected for the entire year
3TC	Lamivudine

CHAPTER 1

1 INTRODUCTION

1.1 HIV infection

1.1.1 Epidemiology of HIV infection.

The acquired immunodeficiency syndrome (AIDS) is caused by the Human Immunodeficiency Virus (HIV)[1-3]. AIDS was first recognised in 1981[4-6]. Today, the magnitude of the global HIV pandemic is immense. By the end of 1999, the United Nations Program on HIV/AIDS estimated that 34.3 million people worldwide were living with HIV infection, including 1.3 million children [7]. More than 95% of these live in resource poor nations of the world, predominantly sub-Saharan Africa (24.5 million people) (Figure 1.1). In 1999, 2.8 million died from AIDS related causes bringing the total number of people who have died from HIV infection since the onset of the epidemic to 18.8 million.

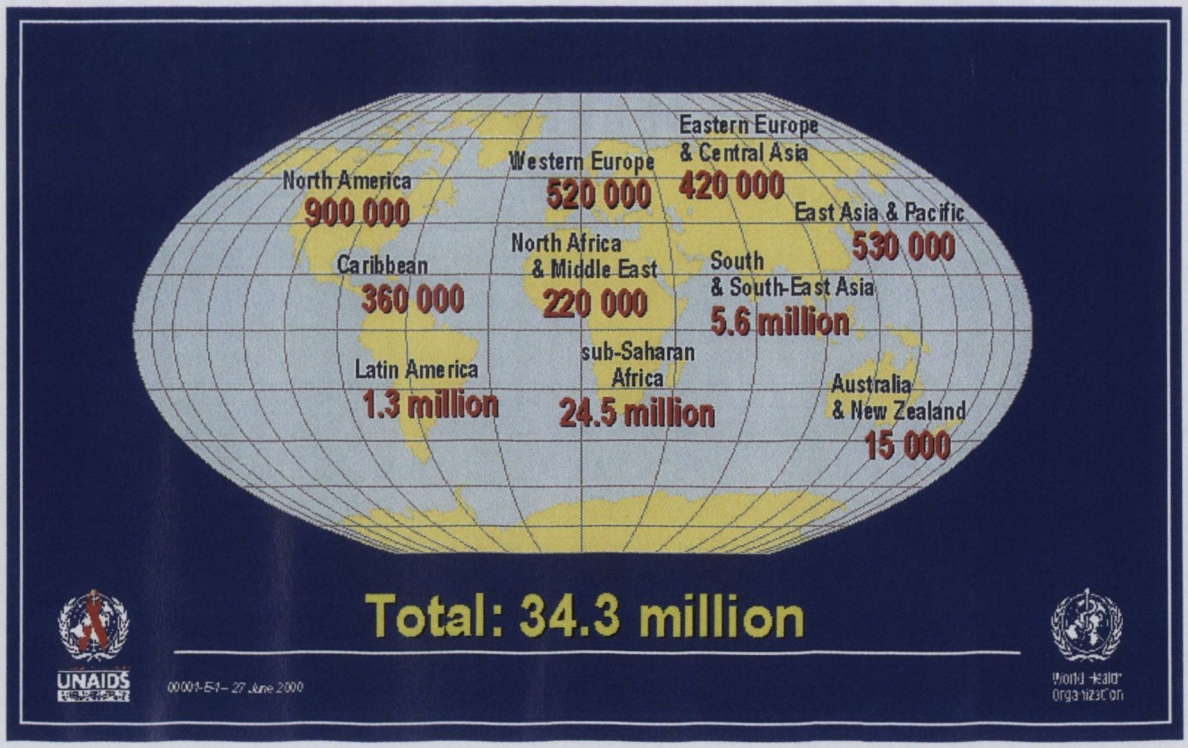


Figure 1.1 UNAIDS estimation of the number of adults and children living with HIV infection at the end of 1999.

Irish data indicate a relatively low incidence of known HIV positivity with approximately 150 new cases per year in a population of 3.6 million [8]. The Irish HIV surveillance

system is based on anonymous confirmatory HIV testing performed centrally at the National Virus Reference Laboratory. The cumulative statistics on HIV infection in Ireland from 1985 to the end of 1999 show that 2,195 cases have tested positive. This includes 691 people who have developed AIDS, of whom 349 have died. Intravenous drug users represent 41.6% of the incident cohort, homosexuals 22.7%, heterosexuals and those whose risk was unspecified 18.8% and the balance (16.9%) is made up of haemophiliacs, children and others [9].

1.1.2 Human immunodeficiency virus

The HIV virus was first identified as the causative agent of AIDS in 1983[1, 2]. It is a single stranded RNA retrovirus, which is distinguished from other viruses by the ability to replicate through a DNA intermediate using a unique enzyme, reverse transcriptase.

The HIV virus infects human cells bearing the CD4 surface marker. The HIV surface protein gp120 binds to the cellular CD4 receptor on susceptible cells, for example helper T-lymphocytes. The HIV reverse transcriptase and RNAase H enzymes convert the viral RNA into double stranded DNA, which is then inserted by the viral integrase enzyme into the genetic material of the cell. Once integrated, the viral genetic material can be transcribed into new RNA when the cell is appropriately stimulated. This process is under the control of viral regulatory proteins, some of which are incorporated along with other RNA molecules into the newly formed viral particles. Viral assembly involves cleavage of these precursor viral proteins by the HIV protease enzyme. The new mature virus particles are now free to infect more helper T-lymphocytes or other cells containing CD4 proteins such as macrophages. The lifecycle of the HIV virus is summarised in Figure 1.2.

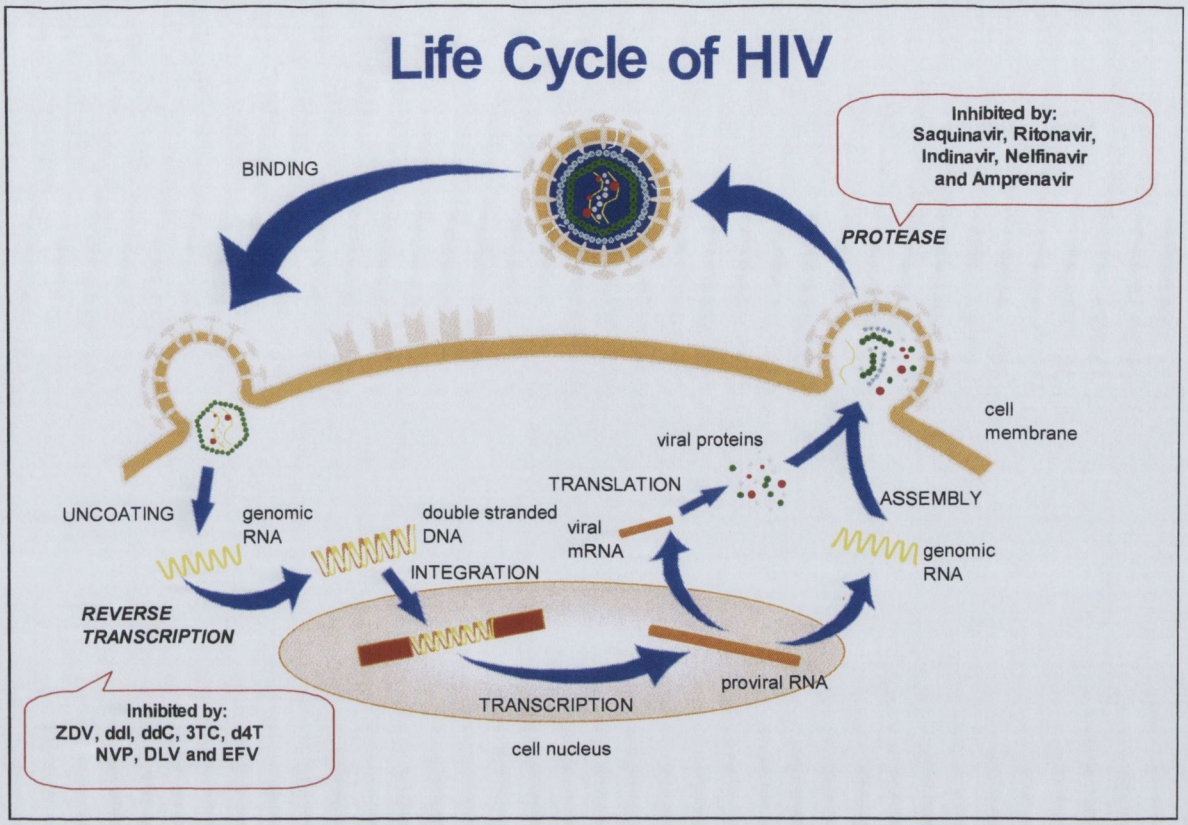


Figure 1.2 Life cycle of HIV

1.1.3 Natural history of HIV infection

HIV infection is usually acquired through either sexual intercourse or exposure to contaminated blood. The clinical course of HIV infection varies widely between individuals. Primary infection, defined as the period when HIV infection is established in the host is characterised in 30-70% of patients by a systemic illness including rash, fever, headache, gastrointestinal upset and lymphadenopathy. Subsequently an asymptomatic phase follows which varies in length before the final phase of the disease. During the asymptomatic phase, the CD4 lymphocyte count declines progressively culminating in the final symptomatic phase, which is characterised by the effects of severe immunodeficiency i.e. AIDS. The progressive loss of CD4 lymphocytes predisposes individuals to a wide range of opportunistic infections and neoplastic disorders, which characterise HIV infection resulting in morbidity and mortality. Viral replication is ongoing during all stages of infection. During primary infection, plasma viraemia is high. During the asymptomatic phase viral replication declines in the plasma but continues at a low level in the lymphoid

tissue resulting in progressive decline in CD4 lymphocytes. During the symptomatic phase the level of viral replication is high. The changes in CD4 cell count and HIV plasma RNA during the clinical course of HIV infection are shown in Figure 1.3.

CDC classification

A system of classifying the stages of HIV infection devised by the Centre for Disease Control (CDC) in Atlanta and modified in 1993 is used at our centre. The classification is based on CD4 cell count and the presence of constitutional symptoms, opportunistic infection and neoplasm. The risk of a number of opportunistic infections increases as the CD4 cell count declines. The CDC classification system for HIV disease is summarised in Appendix I [10]. By this classification, AIDS is diagnosed on the basis of the presentation of one of a number of specific characteristic opportunistic infections also listed in Appendix I

Opportunistic disease.

HIV infection is characterised by progressive loss of CD4 lymphocytes and diminished immune response to opportunistic infection. It has long been recognised that there is a strong relationship between declining CD4 cell counts and the risk of specific opportunistic infections [11]. The opportunistic infections commonly occurring in HIV disease are summarised in the CDC classification of HIV disease (Appendix I). There has been a dramatic decline in the incidence of opportunistic infection in the developed world subsequent to intensification of antiretroviral therapy and at least partial recovery of immune function. In the USA, Palella *et al* demonstrated a marked decrease in morbidity and mortality associated with antiretroviral therapy in severely immunosuppressed patients ($CD4 < 100 \times 10^6/L$)[12]. Mortality decreased from 29.4 per 100 person years in 1995 to 8.8 per 100 person years in the second quarter of 1997. The incidence of three major opportunistic infections, PCP, MAC or CMV fell from 21.9 per 100 person years to 3.7 per 100 person years by mid-1997. Rates of prophylaxis for MAC and PCP remained constant

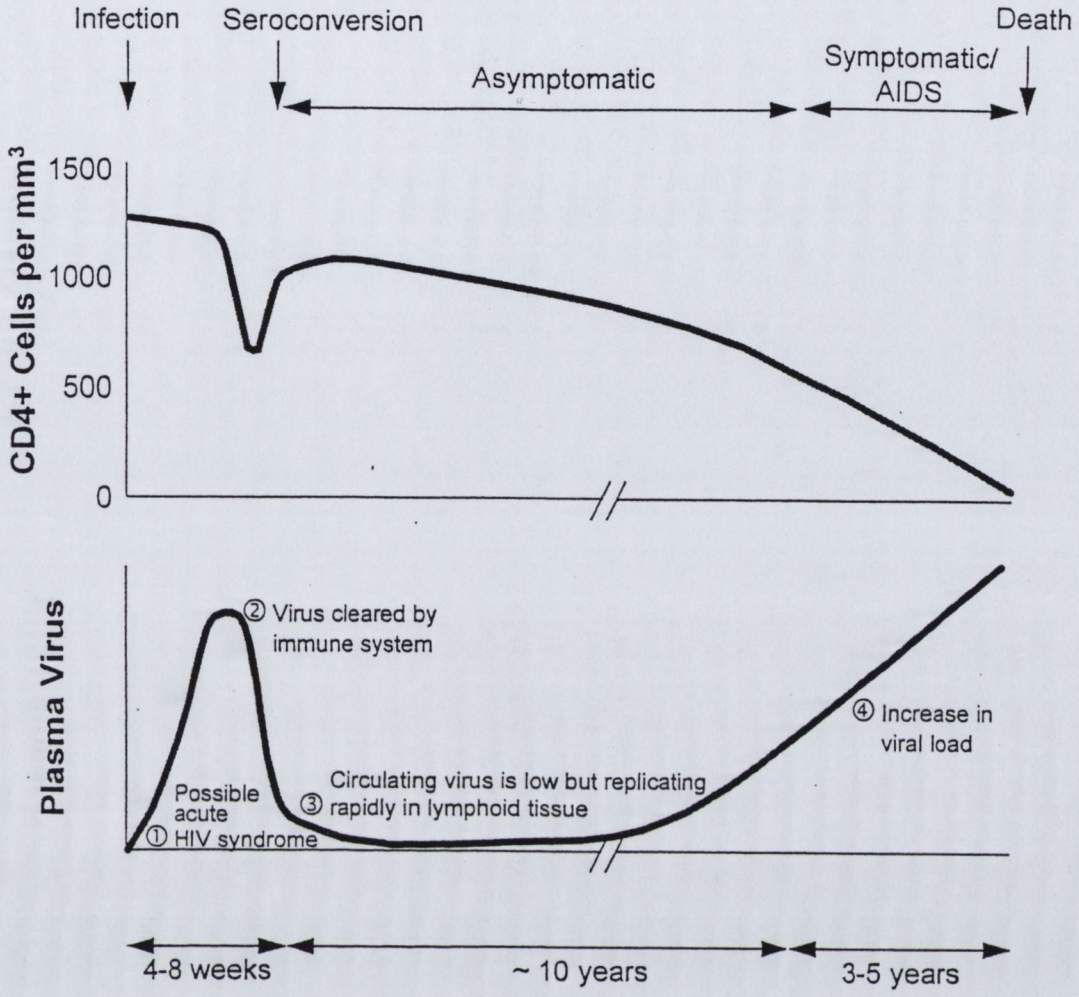


Figure 1.3 **The natural history of HIV infection.**

throughout the study. Increased intensity of antiretroviral therapy was associated with a stepwise reduction in morbidity and mortality. Combination therapy was associated with the greatest reduction; inclusion of a protease inhibitor appeared to confer extra benefit. In a similar study in San Francisco General Hospital, dramatic decreases in the incidence of newly diagnosed opportunistic infections were reported following the availability of HAART late in 1995[13]. From 1994 to 1997 the following decrease in the incidence of opportunistic infections were noted: 71.4% for PCP, 93.8% in CMV retinitis, 83.6% in MAC-positive microbiological cultures and 63% decrease in cryptococcal meningitis. The largest decrease in new opportunistic infections occurred between 1996 and 1997 corresponding to a 30% increase in protease inhibitor use in this cohort.

1.2 Antiretroviral therapy

1.2.1 Antiretroviral agents

Clinically effective agents have been developed against two of the stages of the HIV lifecycle i.e. reverse transcription and viral assembly. Currently there are 3 classes of antiretroviral agents, which include 14 individual drugs, available in Ireland. Details of these antiretroviral agents including class, daily administration schedule and drug acquisition cost for 1 year's treatment are summarised in Table 1.1.

1.2.2 Use of antiretroviral therapy.

Zidovudine was the first antiretroviral agent to be licensed in 1987. This agent had demonstrated clinical benefit initially in patients with advanced disease (AIDS) and subsequently in patients with less advanced disease i.e. CD4 $< 500 \times 10^6$/L [14-16]. However, it became evident that the antiviral efficacy of zidovudine monotherapy was limited to 1 to 2 years [17, 18], which led to the suspicion that this finding could be explained by the emergence of resistant virus. In 1996, the first unequivocal evidence of

Table 1.1 Antiretroviral agents available in Ireland up to June 1999.

Drug	Antiretroviral class	Daily administration schedule	Annual cost of therapy (IR£)
Zidovudine (ZDV)	Nucleoside reverse transcriptase inhibitor	250mg bd	2014.44
		300mg bd	2417.27
Stavudine (d4T)	Nucleoside reverse transcriptase inhibitor	30mg bd if <60 kg	2408.87
		40mg bd if ≥60kg	2492.95
Lamivudine (3TC)	Nucleoside reverse transcriptase inhibitor	150mg bd	1991.44
Didanosine (ddI)	Nucleoside reverse transcriptase inhibitor	250mg od if < 60kg	1359.19
		400mg od if ≥ 60kg	2188.30
Zalcitabine (ddC)	Nucleoside reverse transcriptase inhibitor	0.75mg tds	1751.45
Abacavir (ABV)	Nucleoside reverse transcriptase inhibitor	300mg bd	3276.85
Nevirapine (NVP)	Non-nucleoside reverse transcriptase inhibitor	200mg bd	2418.13
Delavirdine (DLV)	Non-nucleoside analogue reverse transcriptase inhibitor	400mg tds	2147.05
Efavirenz (EFV)	Non-nucleoside analogue reverse transcriptase	600mg od	3382.09
$Saquinavir_{hgc}$ (SQV_{hgc})	Protease inhibitor	600mg tds	4170.25
$Saquinavir_{sgc}$ (SQV_{sgc})	Protease inhibitor	1200mg tds	3625.54
Indinavir (IDV)	Protease inhibitor	800mg tds	3315.05
Ritonavir (RTV)	Protease inhibitor	600mg bd	4762.73
Nelfinavir (NFV)	Protease inhibitor	750mg tds	4170.25
		1250mg bd	4633.61
Amprenavir(AMP)	Protease inhibitor	1200mg bd	4402.12

the superiority of combination therapy over monotherapy was published. Two large randomised double blind trials, the AIDS Clinical Trials Group (ACTG) study 175 and the Delta study, demonstrated the superiority of dual combination therapy in extending survival and delaying disease progression [19, 20]. The Caesar study published in 1997 added further weight to the combination therapy approach [21]. The rationale for combination therapy is based on a decreased opportunity for the development of drug resistance, an ability to target different stages of the HIV life cycle (divergent therapy), and the possibility of targeting different cellular reservoirs (resting or stimulated cells) or tissue reservoirs of HIV, for example the brain. Since the information from these trials was available to the scientific community in advance of publication, the treatment paradigm began to shift from sequential monotherapy to dual combination therapy from the beginning of 1995.

During 1996, three events further radically changed the treatment of HIV infection i.e. the advent of a range of potent antiretrovirals, the availability of HIV RNA assays and the new antiretroviral strategy "Hit early, Hit hard" that was adopted subsequent to the XIth World HIV conference in Vancouver in the Summer of that year. The protease inhibitors constituted a new class of antiretrovirals that became available for use in clinical practice in Ireland in 1996. These agents target the protease enzyme, which is essential in the life cycle of the HIV virus for the production of infectious virions. The novel site of action of these drugs and their unique ability to target both chronically and acutely infected cells make them an attractive therapeutic option. Saquinavir was the first protease inhibitor to become available in Ireland, in March 1996, followed by ritonavir and indinavir. Stavudine, a new reverse transcriptase inhibitor also became available that year. With the advent of the protease inhibitors, divergent combination therapy involving three drugs usually two nucleoside analogues and a protease inhibitor soon became standard of care.

The viral load assay, which became available in August 1996, facilitated more accurate estimation of disease progression and response to antiretroviral therapy than had been previously possible with CD4 cell counts alone [22-27]. Prior to 1996 at our centre, antiretroviral therapy had been reserved for patients in the most advanced stage of disease with either a CD4 cell count < 200 x 10^6/L and/or a history of an AIDS defining illness i.e. Stage C disease. Following review of new data, the old concept of viral latency in asymptomatic HIV-infected individuals was revised and a strategy of "Hit early, Hit hard" was advocated [28]. Mathematical modelling had demonstrated that there is an ongoing high level of HIV replication driving a rapid turnover of CD4 lymphocytes at all stages of infection [29-31]. Continuous HIV replication results in continuous mutations thus leading to increasing viral diversity. Fully suppressing viral replication with therapy may be therefore easier in the earlier stages of disease [32]. In addition, HIV disease is associated with progressive loss of CD4 cells. Complete immune reconstitution may prove impossible for patients with advanced disease. Therefore therapy may be more beneficial if instituted prior to the development of substantial immune defects [32]. As a consequence, the criteria for initiation of antiretroviral therapy were altered to encompass individuals with CD4 cell count < 350-500 x 10^6/L and HIV plasma RNA >10,000 copies/ml. This new strategy was facilitated by a rapid increase in the number of antiretroviral agents available to treat HIV infection from 1996 on. Strategies for initiation of antiretroviral therapy before and after summer 1996 are summarised in Table 1.2.

Table 1.2 Recommendations for initiation of antiretroviral therapy before and after XIth World HIV Conference, July 1996

Disease indicator	Pre-July 1996	July 1996 on
HIV RNA	N/A	HIV RNA > 5,000 to 10,000 copies per ml.
CD4 cell count	≤ 200 x 10^6/L	Consider treatment at all CD4 cell counts particularly if < 500 x 10^6/L Treatment maybe deferred if CD4 cell counts are stable between 350 and 500 x 10^6/L and plasma HIV RNA levels < 5,000 to 10,000 copies per ml. Treatment also indicated for rapidly declining counts > 300 x 10^6/L over 12 months.
Clinical symptoms	AIDS defining illnesses	HIV-related symptoms

Another new class of antiretrovirals, the non-nucleoside reverse transcriptase inhibitors, became available in Ireland in 1997. This class including nevirapine, delavirdine and efavirenz, has the same target as the nucleoside analogues but has a different site of action. There are currently 14 antiretroviral agents available and therefore selection of combination regimens is complex. A number of triple drug combinations have been recommended for initial therapy in treatment naive patients (Table 1.3). Salvage regimens prescribed for patients who have failed to respond to initial therapy may include an even greater number of antiretrovirals. Selection of agents for use in combination is limited by pharmacological interactions, overlapping toxicity and resistance and cross-resistance profiles of the constituents. Therapy is individualised to the patient taking consideration of the likely resistance profile of the virus based on a knowledge of previous antiretroviral exposure, the patient's ability to adhere to the regimen, in addition to substantial drug-drug and drug-disease interactions. Recently genotypic resistance profile assays have become available in Ireland, which can further aid the selection of suitable antiretroviral combinations [9]. Such regimens have become known as Highly Active Antiretroviral

Therapy (HAART) because of unprecedented improvement in surrogate markers of disease progression and clinical end point data that has been associated with their use.

The ultimate goal of antiretroviral therapy is substantial and durable suppression of viral replication in all viral compartments. The rationale for this aim is the observation that there is a strong positive correlation between the viral load plateau concentration (viral set point) and the rate of disease progression or death [22]. The optimal treatment response is reduction of plasma viral RNA to below the level of detection of the current HIV RNA assay.

Table 1.3 Potential HAART regimens for initial therapy and alternative regimens for treatment failure.

Initial regimen	Alternative regimen
ZDV + ddI + NFV	d4T +3TC + IDV d4T +3TC + EFV d4T +3TC + RTV + SQV
ZDV + 3TC + NFV	d4T + ddI + IDV d4T + ddI + NVP RTV + SQV + d4T
d4T + 3TC + NFV	ZDV + ddI + IDV ZDV + ddI + EFV RTV + SQV + ZDV
d4T + ddI + EFV	d4T +3TC + NFV ZDV + 3TC + IND
ZDV + ddI + ABV	d4T + ddI + EFV d4T + ddI + NFV

1.2.3 Tolerability of antiretroviral therapy

Licensing of the first antiretroviral agent zidovudine was undertaken with unprecedented haste. Licensing by the Federal Drugs Administration (FDA) was based on a small number of trials of limited duration, which had demonstrated the short-term safety and efficacy of zidovudine [14, 15]. In the five-month interim period between these trials and approval, zidovudine was made available on a compassionate release programme to individuals with advanced disease. Acceleration of the approval process for new therapeutic agents has become commonplace in HIV infection because of the devastating nature of the disease and the dearth of effective antiviral agents [33]. However, as a consequence of acceleration of the approval process, data on long term safety and the incidence of rarely occurring adverse effects may not be available at time of licensing [34]. Subsequent to licensure, a number of long term or rare adverse events have been recognised in association with the protease inhibitors including new onset or exacerbation of pre-existing diabetes mellitus, increased bleeding tendency in haemophiliacs and lipodystrophy syndrome etc. Post-marketing surveillance of the toxicity of these agents is therefore of paramount importance to complete the tolerability profiles of these effective agents. A comprehensive knowledge of the adverse events associated with an antiretroviral agent, facilitates analysis of the risk-benefit ratio, aids in selection of the constituents of a combination regimen and increases the likelihood of a successful therapeutic response.

1.3 Pharmacoepidemiology & Pharmacoeconomics

1.3.1 Pharmacoepidemiology

The Greek physician, Hippocrates used the word 'epidemeion' 2,400 years ago in reference to diseases that "visit" the community. The English word 'epidemiology' was first used in the 1850's. Epidemiology is defined as the basic quantitative science of public health directed at the empirical study of health and diseases within populations.

Pharmacoepidemiology is the application of the basic principles of epidemiology to the study of drug use. The term pharmacoepidemiology was coined in the early 1980's to explicitly describe the study (usually post-marketing) of adverse drug reactions. Pharmacoepidemiology has since expanded beyond the area of drug toxicity alone to include more comprehensive questions regarding the use and effects of drugs at an individual and population level. By relating the risks associated with taking medicines to the benefits to be obtained from treatment, and quantifying more precisely the incidence of both immediate and delayed beneficial and adverse effects, pharmacoepidemiological studies may supplement information obtained from clinical trials. As healthcare systems become subject to increasing cost constraints and medicines become more expensive, pharmacoepidemiological techniques have contributed to the assessment of the economic implications and consequences of prescribing.

1.3.2 Pharmacoeconomics

The increasing age of developed countries' populations, the primacy of drug therapy in medical practice, the rapid expansion of the absolute number of drug therapies and the increasing numbers of drugs taken in combination have increased health budgets world-wide. Health expenditure is now approximately 8% of the world's total gross national product [35]. In Ireland, healthcare spending represented approximately 6.1% of the gross domestic product in 1996 [36]. As total healthcare spending increases throughout the world, it has become imperative to demonstrate that medical interventions, including new pharmaceuticals provide adequate value [37]. The relatively new scientific discipline of pharmacoeconomics is a branch of health economics that focuses on the costs and benefits of drug treatments. Pharmacoeconomic evaluations may encompass aspects of economics, clinical evaluation, epidemiology, decision theory, bio statistics and psychometrics. The Irish National Centre for Pharmacoeconomics was established in 1998 with financial support from the Department of Health and Children [36]. Its aim is to promote the

advancement of the discipline of pharmacoeconomics through practice, research and education. The research focus of the centre is the economic analyses of high cost areas. High cost therapeutic areas arise either as a result of the 'product mix' i.e. the prescribing of newer more expensive medications or a 'volume' effect i.e. the growth in the absolute number of prescription items.

Economics is the language of scarcity and choice. It gives an awareness of the resource dimension of the difficult decisions, which are increasingly necessary in a health service faced with unlimited demand for its services but possessed of limited resources to meet these demands. Economics can be seen as a mechanistic approach to sensitive issues, but clarification of the resource implications of different choices makes better decision making possible. As resources are limited, timely and relevant information about the costs and outcomes helps to move the health system towards the maximum health impact of a given budget.

1.4 Specialist HIV care in Ireland

1.4.1 Genito-Urinary Medicine Clinic, St James's Hospital, Dublin.

St James's Hospital is the largest university teaching hospital in Ireland and houses the national referral centre for management of HIV infection. Specialist care is provided by a dedicated multidisciplinary team comprising medical, nursing, and paramedical staff including pharmacists, a clinical nutritionist and medical social workers. This team provides both inpatient and outpatient care for HIV-infected individuals and patients with other sexually transmitted diseases.

Outpatient care for HIV patients is provided during two scheduled outpatient clinics. There is a dedicated day ward located in the genitourinary medicine clinic. Here, scheduled administration of chemotherapy and other pharmacotherapy takes place in addition to

emergency review for acutely unwell HIV-infected patients. Most inpatient admissions are referred from the day ward or via the day ward from the outpatient clinics. Inpatient care is provided in a dedicated ward and HIV-infected individuals may be admitted for non HIV-related diagnoses, for example endocarditis secondary to intravenous drug use, in addition to HIV-related indications. All HIV-related medication including antiretroviral therapy and pharmacotherapy of opportunistic disease and other complications of HIV infection is dispensed from the satellite pharmacy located in the outpatient clinic either following medical review at an outpatient attendance or on discharge following inpatient admission. There are now three other centres in the country providing specialist care to HIV-infected adults in addition to one paediatric centre. Nevertheless, the majority of infected individuals receiving specialist care in Ireland attend St. James's Hospital, Dublin.

1.4.2 Funding of specialist HIV care

Outpatient and inpatient care for HIV infection, in common with certain other infectious diseases is available free of charge to all infected individuals in Ireland [38]. Patients may opt for private care if desired. Private inpatient care is provided on private wards in the public hospital by the same medical team who cares for the public inpatients. Private healthcare may be paid for directly by the patient. More commonly patients contribute to a private insurance company, which then subsidises the majority of inpatient and outpatient costs. All patients regardless of private insurance status receive all HIV-related medication free of charge. The majority of HIV-infected individuals at our centre avail of publicly financed inpatient and outpatient services.

The Department of Health and Children is directly responsible for funding the majority of HIV healthcare related expenditure. The specialist hospitals receive a budget allocation from the Department of Health and Children for provision of HIV services. In addition the hospital's budget may be adjusted by up to 1% based on the previous year's inpatient

casemix index [39]. In accordance with the casemix model, all admissions are assigned a Diagnosis Related Group classification (DRG). Linking the relative value assigned to each DRG with costing data provided by the Department of Health and Children's speciality costing program provides an estimation of the hospital's total resource consumption. The DRG prospective part payment system provides an alternative to individual data collection for the assignment of a proportion of the hospital's budget based on the complexity of its casemix. There are three DRGs specific to HIV disease, all of which are associated with high relative value. However it is worth noting that an admission may be coded as an alternative DRG with a smaller relative value if it is considered to more accurately reflect resource consumption. Accurate DRG coding of a hospital's admissions is important to ensure adequate funding in the future. The relative value assigned to specific DRGs is based on resource consumption and costing data derived from US hospitals with some modification for costs within our healthcare system. Few studies have been published to date, which investigate how accurately costs associated with DRGs reflect actual expenditure in Irish hospitals.

All HIV-related medication is dispensed from the satellite pharmacy located in the outpatient clinic. Dispensing fees and profit margins charged by private community pharmacies are avoided. The Department of Health and Children provides funding of outpatient pharmacotherapy on an anonymous individual patient basis through the auspices of the domicillary health board in which the individual resides.

Both inpatient and outpatient care including outpatient drug therapy is provided by our hospital. Therefore, it is possible to conduct a cost of illness study to calculate total expenditure on provision of HIV care from the perspective of the healthcare service. To date no attempt has been made to calculate the cost of HIV disease within the Irish healthcare system.

Such cost of illness studies are useful for [40]:

- providing information on the burden of a specific disease.
- incorporation into cost effectiveness evaluations, for example to compare more than one intervention for a specific disease or to compare interventions in the management of different diseases.
- clarifying the most important cost components in the treatment of a specific disease.
- explaining recent trends in costs and/or projecting future disease costs based on demographic, epidemiological and technological change.

The management of HIV disease has changed rapidly over the last decade with the enlargement of the antiretroviral armamentarium, improved understanding of viral dynamics and expansion of the criteria for initiation of antiretroviral therapy. The adoption of HAART as standard of care has been likened in magnitude to the discovery of penicillin such is the observed therapeutic impact in converting HIV disease from an acute presentation with short prognosis to a chronic disease manageable with appropriate pharmacotherapy. As a consequence, the pharmacoepidemiology and pharmacoeconomics of HIV disease have changed substantially. Prior to this study, no attempt had been made to characterise the active cohort of HIV-infected individuals attending our service or to determine the total cost of providing HIV care from the healthcare perspective.

1.5 Aims of the thesis

The HIV pandemic has resulted in the most intense and as yet unparalleled effort devoted to antimicrobial drug development ever to be initiated in the developed world [41]. In the USA and Europe, steps have been taken to expedite the formal licensing of new drugs. Licenses for antiretroviral drugs in the USA have been granted on surrogate marker data with a requirement for clinical data to be provided within a year, while in Europe antiretrovirals are licensed through a centralised procedure since January 1995 [33]. Furthermore, in the performance of early antiretroviral studies, administrative officials in

concert with regulatory authorities have deemed it important to provide access to medication with parallel track drug development [41]. These expanded access schemes are designed for people who are unable to participate in trials or who are excluded by the study protocol or whose medical situation justifies immediate intervention [42]. This approach allows patients to avail of new treatments following the completion of basic pharmacokinetic and toxicity studies but prior to the realisation of long term clinical studies designed to guide clinicians in the optimal use of these drugs. The accelerated release of drugs is undoubtedly helpful in terms of drug provision. However, it may in turn result in other clinical challenges, as the more subtle aspects of tolerability profiles may not be available for some time. Collection of such data is for the greater part reliant on post marketing surveillance studies.

The rapid enlargement in the antiretroviral armamentarium and the primacy of drug therapy, in conjunction with the expansion of the criteria for initiation of antiretroviral therapy has resulted in increased expenditure on the management of HIV-infected individuals. As total healthcare spending increases throughout the world, greater emphasis is being placed on research, which demonstrates value for medical interventions including new and existing pharmaceuticals. Pharmacoeconomics is that branch of health economics that focuses on the costs and benefits associated with drug therapy particularly high-cost areas. Pharmacoeconomic evaluations can assist manufacturers, clinicians, governmental agencies, policy-makers and consumers to make informed, appropriate decisions about adoption and application of medication regimens. Adoption of HAART as standard of care is associated with high drug acquisition costs and therefore constitutes an appropriate area for pharmacoeconomic analysis.

This thesis is an observational study of the impact of HAART in an Irish clinical cohort. The aim of this thesis is to assess the impact of HAART on the pharmacoepidemiology and pharmacoeconomics of HIV infection in Ireland. This thesis requires the construction of an

observational cohort database including demographic and clinical outcome data spanning the period prior to and subsequent to the adoption of HAART as standard of care. The impact of HAART on outpatient expenditure on pharmacotherapy of four of the most common and most expensive opportunistic infections associated with HIV disease in our cohort is examined in detail. The total cost of providing specialist care to HIV infected individuals from the healthcare provider perspective is determined for each year of the study period. As no detailed validated data for HIV inpatient costs was available prior to this study, a microcosting determination of the cost of inpatient care is undertaken. The non-monetary impact of HAART is addressed by the construction of comparative tolerability profiles for the currently available protease inhibitors following a review of the literature. In addition, a prospective surveillance study of drug toxicity associated with protease inhibitors in the cohort at St. James's Hospital is presented. Finally, an overall discussion addresses the major findings from this research, their relevance to practice in Ireland and beyond and highlights a number of potential assumptions for pharmacoeconomic evaluation of HIV disease which have been validated or refuted by this study. The final chapter also includes a dissertation on the advantages and limitations of observational databases in measuring the clinical and economic impact of new therapeutic strategies.

CHAPTER 2

2 IMPACT OF HAART ON THE EPIDEMIOLOGY OF HIV INFECTION IN IRELAND

2.1 Introduction

Initial clinical trials used to attain early licensure for the protease inhibitors, demonstrated immunological and virological benefit associated with HAART [43, 44]. Although the immunological and virological success rates evident in clinical trials may not always apply in the clinical setting, it is generally accepted that effect on viral load and CD4 cell count reflects clinical efficacy [24, 45]. Few large studies have included clinical end point data such as progression to AIDS and mortality. Such long-term outcomes require studies of prolonged duration. In the absence of trials assessing clinical endpoints, observational data has been used to examine the impact of HAART on clinical progression. A number of observational cohort studies have reported reduced mortality, hospitalisation rate and incidence of opportunistic infection following the introduction of HAART as standard of care [46-49]. Differences, which may exist between cohorts include variations in demographics, access to health care, availability of HAART and prescribing patterns. The EuroSIDA study has previously demonstrated variation in response to antiretroviral therapy dependent on geographical location within Europe [50].

Our clinical cohort represents the majority of individuals who attend HIV services in Ireland and includes intravenous drug users, homosexual men, heterosexuals and haemophiliacs as well as many women. Therefore, our cohort may be considered representative of the national cohort as our demographic characteristics mirror the national statistics. Characterising the impact of HAART on surrogate markers and clinical endpoints requires a comprehensive database including patient demographics and clinical details. No such database was available in Ireland prior to this project. Although the total number of patients who had ever attended the service was known, the "active" cohort at any time point i.e. patients attending regularly for ongoing care, could not be easily

determined. Quantification of the active cohort during specific time periods is necessary to calculate the rate of occurrence of clinical events.

2.2 Aim

The aim of this chapter was to evaluate the impact of HAART on the natural history of HIV infection in this Irish cohort. The demographic characteristics of the cohort over the study period were determined. Changes in the immunological and virological profile of the cohort over the study period were determined. In addition, changes in clinical end point data were determined including mortality rate, cause of death, hospitalisation rate, discharge diagnoses, incidence and nature of AIDS defining illnesses, and HIV disease progression rate.

2.3 Method

2.3.1 Data collection

Data was abstracted from a number of information sources including the administrative system in the HIV clinic and databases in the laboratory, pharmacy and hospital administration. To date, these databases which were designed principally for administrative purposes are discrete and therefore information on individual patients taken from each system was collated in a single spreadsheet using the hospital medical record number as a unique identifier. A retrospective review of all patients' medical notes was undertaken in conjunction with a senior clinician, as some data including information on staging, details of opportunistic infection, and detailed discharge diagnoses for hospital admissions were not recorded elsewhere. Additional survival data was obtained from the hospice homecare team, the clinic counsellors and the state coroner's office.

2.3.2 Data analysis

The data was then collated to construct an electronic database in a format that could be analysed using the software packages Excel® version 7.0 (Microsoft Inc.) and JMP® version 3.2.1 (SAS Institute Inc.). For the purposes of this analysis, data was censored on the last day of June 1999. Data from the first two quartiles of 1999 is termed 1999*. This data was used to calculate projected event rates for the entire year identified as 1999^{proj}. Data was analysed either per calendar quartile or per calendar year as appropriate from January 1995 onwards. To facilitate comparison with the literature, incidence of events was calculated using a person-years analysis. Incidence rates were calculated by dividing the number of events by the number of active patient years of follow-up. To examine trends in our own data set, annual event rates were compared. To determine changes in the demographic characteristics of the cohort over the study period, pairs of categorical variables were cross-tabulated and tested for association using the Pearson's Chi Squared Test.

2.3.3 Active cohort and new attendees

Patient follow-up began either on the first day of the study period or the day first registered at the clinic, which ever was the later date. The patient was then included in follow-up for the time period that he or she was considered to be a member of the active cohort. Attendance at the HIV service every six months was considered minimum standard of care. Patients were defined as being members of the active cohort in a particular quartile if they had attended the HIV service during that quartile or during either of the two previous quartiles. A patient who had not attended for two consecutive quartiles was deemed discharged from the active cohort in the third quartile and remained so until the next attendance. Patients who died or transferred care to another clinic were eliminated from analysis from the quartile in which they died or transferred care. Attending the HIV service was defined as an outpatient visit, inpatient or day ward admission, receipt of medication

or laboratory evaluation. Using this definition, a JMP® program was designed to determine the number of active patients and the number of person years of follow-up for each quartile of the study period. Trends in demographics were examined. New attendees were defined as those who attended our HIV services for the first time. The number and demographics of new attendees were determined.

2.3.4 Mortality

Mortality rate was expressed as number of deaths per 100 patient years per quartile and per annum. Mortality rates according to gender, risk factor for acquisition of HIV and stage of HIV disease were also calculated.

2.3.5 Immunology and virology

The immunological profile of the cohort over the study period was determined as follows. CD4 cell counts were stratified into the following categories: $< 50 \times 10^6$/L, 50 - 100 x 10^6/L, 101 - 200 x 10^6/L, 201-500 x 10^6/L and $> 500 \times 10^6$/L. If a patient had more than one CD4 cell count during a particular quartile, the lowest value recorded was taken. Using JMP®, an immunological profile for the cohort over the study period was constructed. Furthermore, the change in the median CD4 cell count of the cohort over the study period was determined by linear regression.

Plasma viral RNA evaluation became available in this country during 1996 coincident with the availability of HAART. The virological profile of the cohort over time was determined with viral load stratified as follows: < 400 copies per ml, 401-10,000 copies per ml, > 10,000 copies per ml. If a patient had more than one viral load measurement in a quartile the highest value was taken. This data was used to construct a virological profile for the active cohort each quartile. Plasma viral RNA was measured initially by the Roche Amplicor® assay with a level of detection of viral RNA of < 400 copies per ml and

subsequently by the Chiron branched DNA Ultra-sensitive® assay with a level of detection of < 50 viral copies per ml resulting in variability in the lower limit of detection of the virus according to the technology used. The proportion of the cohort with a viral load below the current level of detection of the virus was also determined. This was calculated by dividing the number of patients with undetectable viral load by the number of patients who had a viral load measurement during that quartile. The change in the median log viral load of the cohort from the time that viral load testing became available until the end of the study period was determined by linear regression analysis. Viral load measurements had a positively skewed distribution. Therefore for linear regression analysis, undetectable values were assigned half the current lower level of detection and the viral load was then log transformed. Only patients who had a CD4 cell count or viral load measurement carried out during a particular quartile contributed to the immunological or virological profile of the cohort during that time period.

2.3.6 CDC stage of HIV disease, AIDS defining illnesses and HIV progression events.

Patients were staged according to the 1993 CDC revised classification system for HIV disease. Data was manipulated using JMP® to calculate the proportion of the cohort in each stage of HIV disease over the study period. Trends in the incidence and nature of newly diagnosed AIDS defining illnesses were examined. Recurrence of disease was not included in this analysis. The incidence of AIDS defining illnesses was expressed as number of new diagnoses per 100 patient years per annum. Disease progression was estimated using a modification of the CDC classification system for HIV disease. Progression events included:

Stage B,

Stage C^1 on the basis of CD4 count < 200 x 10^6/L or first AIDS defining illness,

Stage C^2 on basis of next AIDS defining illness,

Stage C^3 on basis of next AIDS defining illness etc.,

Stage D, death.

Only progression events, which occurred at least one quartile subsequent to the initial quartile of registration, were included. Progression rate was expressed as number of progression events per 100 patient years per quartile and per annum.

2.3.7 Hospitalisation

Hospital admission rates, numbers of inpatient days and mean length of stay were calculated. Discharge diagnoses were coded in accordance with Appendix II. Categories included specific AIDS defining illnesses, bleeding complications in haemophiliacs, adverse drug reactions, complications of intravenous drug use, for example deep venous thrombosis etc. Trends in discharge diagnoses over the study period were examined.

2.3.8 Outpatient contacts

Trends in attendance at the outpatient clinic and day ward were examined. The number of outpatient contacts was derived from the clinic administration database. As accurate data on attendance was only available from September of 1995 onwards, therefore attendance for 1995 was extrapolated from data for the last four months of that year.

2.3.9 Antiretroviral therapy

Proportion of patients each quartile treated with antiretroviral therapy was calculated. Antiretroviral therapy was classified as monotherapy, dual therapy, and varieties of HAART i.e. combination therapy with 3 or more drugs including one or more of the following: protease inhibitors, non-nucleoside reverse transcriptase inhibitors, or the nucleoside reverse transcriptase inhibitor abacavir:

- **HAART-P:** HAART including one or more protease inhibitors
- **HAART-R:** HAART including reverse transcriptase inhibitors only
- **HAART-PN:** HAART including a protease inhibitor plus a non-nucleoside reverse transcriptase inhibitor

A treatment regimen was only assigned to a particular quartile if the patient had received treatment for at least 30 days during that quartile or if during that quartile they terminated a treatment regimen that had lasted for at least 30 days. If a patient received more than one regimen during a quartile, only the most recent one was included in the analysis for that quartile.

2.4 Results

777 HIV-infected patients who attended the HIV service between the first day of 1995 and the last day of June 1999 were included in the final analysis. The number of active patients under follow-up each quartile increased rapidly over the study period almost doubling from 261 in the first quartile of 1995 to 518 in the second quartile of 1999. Three hundred and seventy-nine patients attended for the first time, 146 died and 38 transferred care to another clinic during the period under review. 1847 patient years were accumulated with a mean follow-up per participant of 2.4 years.

2.4.1 Active cohort

Active cohort demographics each year are summarised in Table 2.1. Statistically significant changes in gender, transmission category, country of birth and disease stage of the active cohort occurred during the study period. The proportion of females increased from 21% in 1995 to 28% by the end of the study ($p < 0.001$). Variations in the proportions of the cohort presumed to have acquired HIV through homosexual contact and through transfusion of contaminated blood products were modest. However, the intravenous drug using proportion decreased from 55.0% in 1995 to 41.8% during the first six months of 1999 accompanied by an increase in the group presumed to have acquired HIV through heterosexual contact from 9.1% to 20.4%. In 1995, the vast majority of the active cohort had been born in Ireland (97.3%). This percentage fell steadily over the study period to

Table 2.1 Demographic characteristics of participants in the active cohort each year – prevalent patients.

		1995	1996	1997	1998	1999*	
Number of patients who attended at least once each year:		420	465	487	538	453	
Number of active patient years:		321	377.25	420.25	460	256	
Number of active patient quartiles:		1284	1509	1681	1840	1024	
Gender:	*Male*	1015 (79.0%)	1171 (77.6%)	1281 (76.2%)	1350 (73.4%)	737 (72%)	
	Female	269 (21.0%)	338 (22.4%)	400 (23.8%)	490 (26.6%)	287 (28%)	p<0.001
Transmission category:	*Homosexual*	369 (28.7%)	424 (28.1%)	503 (29.9%)	566 (30.8%)	312 (30.5%)	
	Intravenous drug use	706 (55.0%)	781 (51.7%)	748 (44.5%)	757 (41.1%)	428 (41.8%)	
	Heterosexual	117 (9.1%)	173 (11.5%)	258 (15.3%)	339 (18.4%)	209 (20.4%)	
	Haemophiliac	87 (6.8%)	118 (7.8%)	151 (9.0%)	140 (7.6%)	59 (5.8%)	
	Other	5 (0.4%)	13 (0.9%)	21 (1.3%)	38 (2.1%)	16 (1.5%)	p<0.0001
Country of birth:	*Ireland*	1248 (97.3%)	1437 (95.2%)	1557 (92.6%)	1656 (90.0%)	909 (88.8%)	
	United Kingdom	12 (0.9%)	26 (1.7%)	23 (1.4%)	35 (1.9%)	22 (2.1%)	
	Other EC country	12 (0.9%)	16 (1.1%)	24 (1.4%)	19 (1.0%)	10 (1.0%)	
	Sub-Saharan Africa	8 (0.6%)	20 (1.3%)	49 (2.9%)	90 (4.9%)	54 (5.3%)	
	Other	4 (0.3%)	10 (0.7%)	28 (1.7%)	40 (2.2%)	29 (2.8%)	p<0.0001
Stage of HIV disease:	*Stage A*	308 (24.0%)	355 (23.6%)	361 (21.5%)	417 (22.7%)	244 (23.8%)	
	Stage B	375 (29.2%)	372 (24.7%)	357 (21.2%)	358 (19.4%)	194 (19.0%)	
	Stage C	600 (46.8%)	779 (51.7%)	962 (57.3%)	1065 (57.9%)	586 (57.2%)	p<0.001

1999*: data for first 2 quartiles of 1999 only.

88.8%. Over this time, the percentage of those born in mainland Europe varied little while the proportion born in UK, sub-Saharan Africa and other countries increased from 0.9%, 0.6% and 0.3% to 2.1%, 5.3% and 2.8% respectively. The proportion of active patients in stage A each year remained constant. Over the study period, the proportion in stage B decreased from 29.2% to 19.0%, while the proportion in stage C increased from 46.8% to 57.2% ($p < 0.001$).

2.4.2 New attendees

Three hundred and seventy-nine HIV-infected patients registered for the first time during the study period. Baseline characteristics of new patients enrolled each year are summarised in Table 2.2. Statistically significant changes in gender and stage of HIV disease of new attendees occurred during the study period. Chi-squared analysis of transmission category and country of birth was unreliable due to the small numbers in individual cells. Fisher's exact test was not computable on a table of this size.

There was a marked increase in the number of new attendees between 1995 and 1996 and again between 1998 and 1999^{proj} i.e. figures for first 6 months of 1999 projected to the end of the year. The proportion of new attendees who were male peaked in 1996 at 86.5% and then fell steadily over the study period to 60.3% in 1999. The percentage of women decreased between 1995 and 1996 but increased in every subsequent year. The number of homosexual new attendees each year varied little over the study period. However proportionally, this transmission group accounted for the largest proportion of new attendees each year until 1999^{proj}. In that year, the proportion of intravenous drug users, which had remained somewhat constant over the previous four years, more than doubled. The number of new haemophiliac patients peaked in 1996. The number of heterosexual new attendees increased each year of the study. In 1995, all newly registered patients were born in the EC, the vast majority in Ireland. From 1996 on the proportion of African born

Table 2.2 Demographic characteristics of participants newly enrolled each year – incident patients.

		1995	1996	1997	1998	1999*	
Number of new attendees:		51	96	90	84	58	
Gender:	*Male*	40 (78.4%)	83 (86.5%)	65 (72.2%)	59 (70.2%)	35 (60.3%)	
	Female	11 (21.6%)	13 (13.5%)	25 (27.8%)	25 (29.8%)	23 (39.7%)	p=0.005
Transmission category:							
	Homosexual	26 (51.0%)	35 (36.4%)	34 (37.8%)	31 (36.9%)	14 (24.1%)	
	Intravenous drug use	11 (21.6%)	17 (17.7%)	17 (18.9%)	19 (22.6%)	29 (50.0%)	
	Heterosexual	11 (21.6%)	18 (18.8%)	26 (28.9%)	28 (33.3%)	15 (25.9%)	
	Haemophiliac	1 (2.0%)	24 (25.0%)	10 (11.1%)	2 (2.4%)	0 (0%)	
	Other	2 (3.8%)	2 (2.1%)	3 (3.3%)	4 (4.8%)	0 (0%)	p⊗<0.0001
Country of birth:	*Ireland*	47 (92.1%)	81 (84.4%)	73 (81.1%)	65 (77.3%)	45 (77.6%)	
	United Kingdom	3 (5.9%)	5 (5.2%)	1 (1.1%)	5 (6.0%)	2 (3.4%)	
	Other EC country	1 (2.0%)	0 (0%)	5 (5.6%)	1 (1.2%)	1 (1.7%)	
	Sub-Saharan Africa	0 (0%)	6 (6.3%)	8 (8.9%)	8 (9.5%)	7 (12.1%)	
	Other	0 (0%)	4 (4.1%)	3 (3.3%)	5 (6.0%)	3 (5.2%)	p⊗=0.9
Stage of HIV disease:	*Stage A*	20 (40.0%)	22 (23.2%)	38 (42.2%)	33 (38.8%)	38 (66.7%)	
	Stage B	11 (22.0%)	17 (17.9%)	20 (22.2%)	14 (16.5%)	4 (7.0%)	
	Stage C	19 (38.0%)	56 (58.9%)	32 (35.6%)	38 (44.7%)	15 (26.3%)	p<0.001

1999*: data for first 2 quartiles of 1999 only.

p⊗: Chi-squared value suspect due to small numbers in individual cells.

patients increased from 6.3% to 12.1%. The proportion of patients born in other countries also increased from 1996 on. Therefore, the proportion of Irish born new attendees declined from 92.1% in 1995 to 77.6% in 1999^{proj}. The proportion of new attendees with stage A HIV disease peaked in 1999^{proj}. The proportion of new attendees with stage C disease peaked in 1996.

2.4.3 Mortality

The mortality rate for the cohort as a whole fell each year from 16.8 per 100 patient years in 1995 to 3.5 per 100 patient years in 1998 but increased again in 1999^{proj}. Demographic characteristics of patients deceased each year are summarised in Table 2.3. A similar decline in mortality was evident amongst both males and females and amongst the three predominant transmission groups i.e. intravenous drug users, homosexual men and heterosexuals. The mortality rate amongst intravenous drug users and homosexual men was greater than amongst the heterosexual transmission group. Only one haemophiliac patient died during the study period. In each year, a higher mortality rate was recorded for patients in the most advanced stage of disease. The mortality rate for patients in each stage of HIV disease fell each year for the first four years of the study. However, the mortality rate of stage C patients was greater in 1999^{proj} than the previous year and amongst stage B patients the highest ever mortality rate was recorded in 1999^{proj}.

2.4.4 Immunology & virology

Immunological and virological results are summarised in Table 2.4. There was a statistically significant linear increase in the median CD4 cell count of the cohort over the study period from 120 x 10^6/L in the first quartile of 1995 to 318 x 10^6/L in the second quartile of 1999 ($p < 0.0001$), (Figure 2.1). The patient group with CD4 cell count < 200 x 10^6/L decreased from 54.0% of all patients with CD4 cell counts measured in 1995 to 28.9% in 1999^{proj}. As a consequence there was an overall increase in the proportions of

Table 2.3 Demographic characteristics of participants in the active cohort who died each year.

Values are numbers(rate per 100 active patient years)

		1995	1996	1997	1998	1999*
Number of deaths :		54	34	25	16	17
Mortality rate per 100 active patient years:		16.8	9.0	5.9	3.5	6.6
Gender:	*Male*	41 (16.6)	31 (10.6)	21 (6.6)	11 (3.3)	13 (7.1)
	Female	13 (19.3)	3 (3.6)	4 (4.0)	5 (4.1)	4 (5.6)
Transmission category:	*Homosexual*	15 (16.3)	13 (12.3)	9 (7.2)	3 (2.1)	4 (5.1)
	Intravenous drug use	37 (21.0)	18 (9.2)	13 (7.0)	11 (5.8)	11 (10.3)
	Heterosexual	2 (6.8)	3 (6.9)	3 (4.7)	1 (1.2)	2 (3.8)
	Haemophiliac	0 (0)	0 (0)	0 (0)	1 (2.9)	0 (0)
	Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stage of HIV disease:	*Stage A*	4 (5.2)	2 (2.3)	1 (1.1)	0 (0)	0 (0)
	Stage B	5 (5.3)	0 (0)	2 (2.2)	1 (1.1)	3 (6.2)
	Stage C	45 (30.0)	32 (16.4)	22 (9.1)	15 (5.6)	14 (9.6)

1999*: data for first 2 quartiles of 1999 only.

Table 2.4 Immunological and virological profile of the active cohort.

	1995	1996	1997	1998	1999*
Immunological profile:					
CD4 >500 x 10^6/L	109 (11.6%)	97 (9.2%)	172 (13.6%)	293 (21.2%)	199 (25.9%)
CD4 201-500 x 10^6/L	324 (34.4%)	431 (40.6%)	579 (45.9%)	648 (47.0%)	347 (45.2%)
CD4 101-200 x 10^6/L	166 (17.6%)	208 (19.6%)	266 (21.1%)	231 (16.7%)	117 (15.3%)
CD4 50-100 x 10^6/L	123 (13.1%)	121 (11.4%)	129 (10.2%)	97 (7.0%)	49 (6.4%)
CD4 < 50 x 10^6/L	219 (23.3%)	204 (19.2%)	116 (9.2%)	111 (8.1%)	55 (7.2%)
Virological profile:					
VL > 10,000 copies per ml	N/A	237 (49.2%)	636 (45.0%)	401 (35.9%)	164 (30.1%)
VL 400 - 10,000 copies per ml	N/A	123 (25.5%)	413 (29.2%)	301 (26.9%)	155 (28.4%)
VL < 400 copies per ml	N/A	122 (25.3%)	365 (25.8%)	416 (37.2%)	226 (41.5%)
VL below limit of detection of the current assay.	N/A	110 (22.8%)	356 (25.2%)	329 (29.4%)	159 (29.2%)

1999*: data for first 2 quartiles of 1999 only.

patients with CD4 cell counts between 201 and 500 x 10^6/L and those with CD4 cell counts > 500 x 10^6/L. The proportion of patients with CD4 cell count in the two lowest groups i.e. <50 x 10^6/L and between 50 and 100 x 10^6/L declined each year. The proportion with CD4 cell count between 100 and 200 x 10^6/L increased from 1995 to 1997 and then decreased. Movement through CD4 cell strata was bi-directional i.e. for individual patients the absolute CD4 cell count rather than nadir CD4 cell count was included.

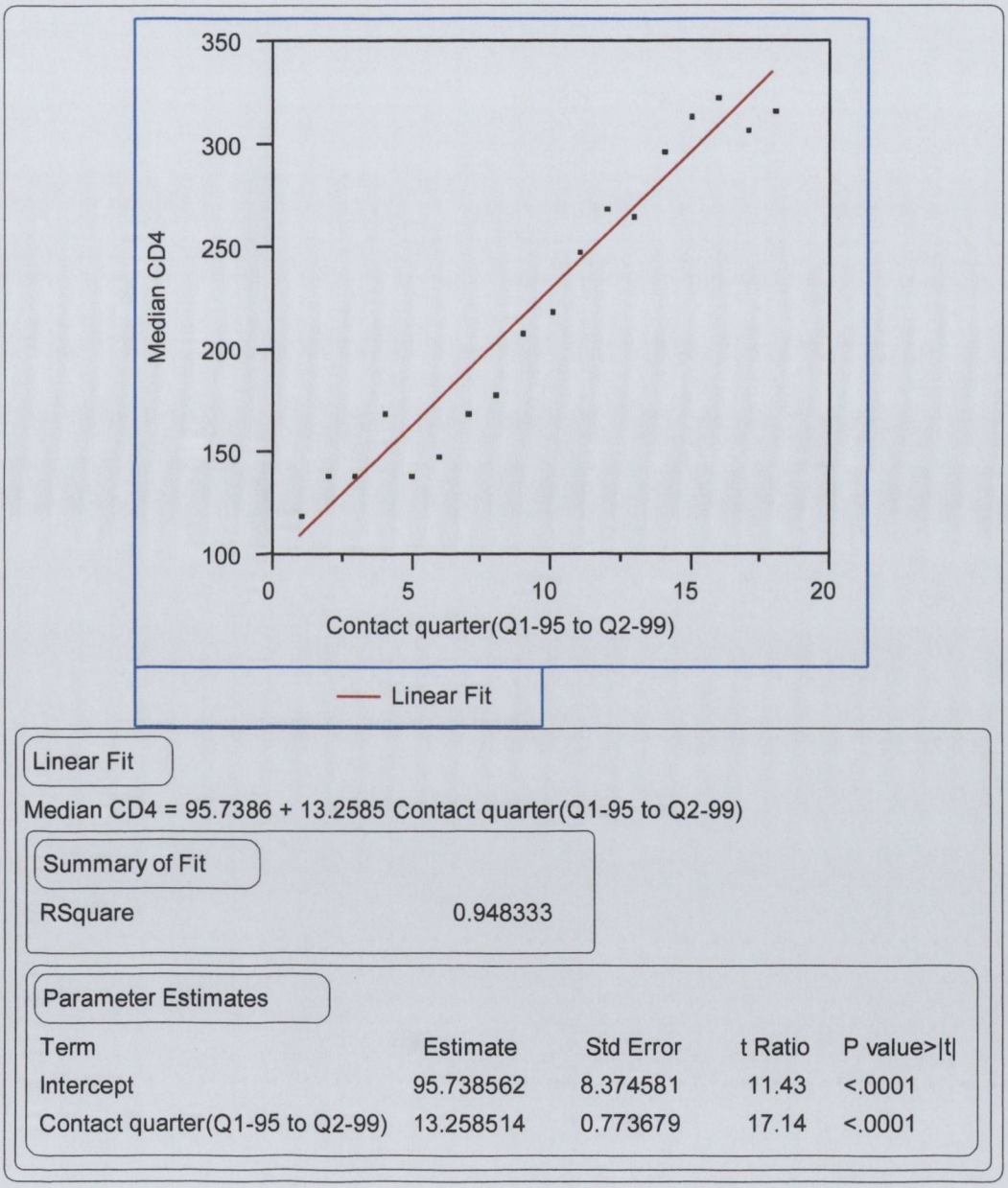


Figure 2.1 The change in median CD4 cell count (x10^6/L) of the active cohort from the first quartile of 1995 to the second quartile of 1999 inclusive.

There was a statistically significant linear decrease in the median log viral load of the cohort from 4.9 log copies/ml in the third quartile of 1996 to 3.4 log copies/ml in the second quartile of 1999 ($p<0.0001$), (Figure 2.2). The proportion of active patients who had a viral load below 400 copies per ml increased from 25.3% in 1996 to 41.5% in 1999^{proj}. The proportion with viral load below the current level of detection of the assay increased from 22.8% in 1996 to 29.2% in 1999^{proj}. Only modest changes were noted in the proportion with viral loads between 400 copies per ml and 10,000 copies per ml. The proportion of active patients with viral burden > 10,000 copies per ml decreased from 49.2% to 30.1% over the study period.

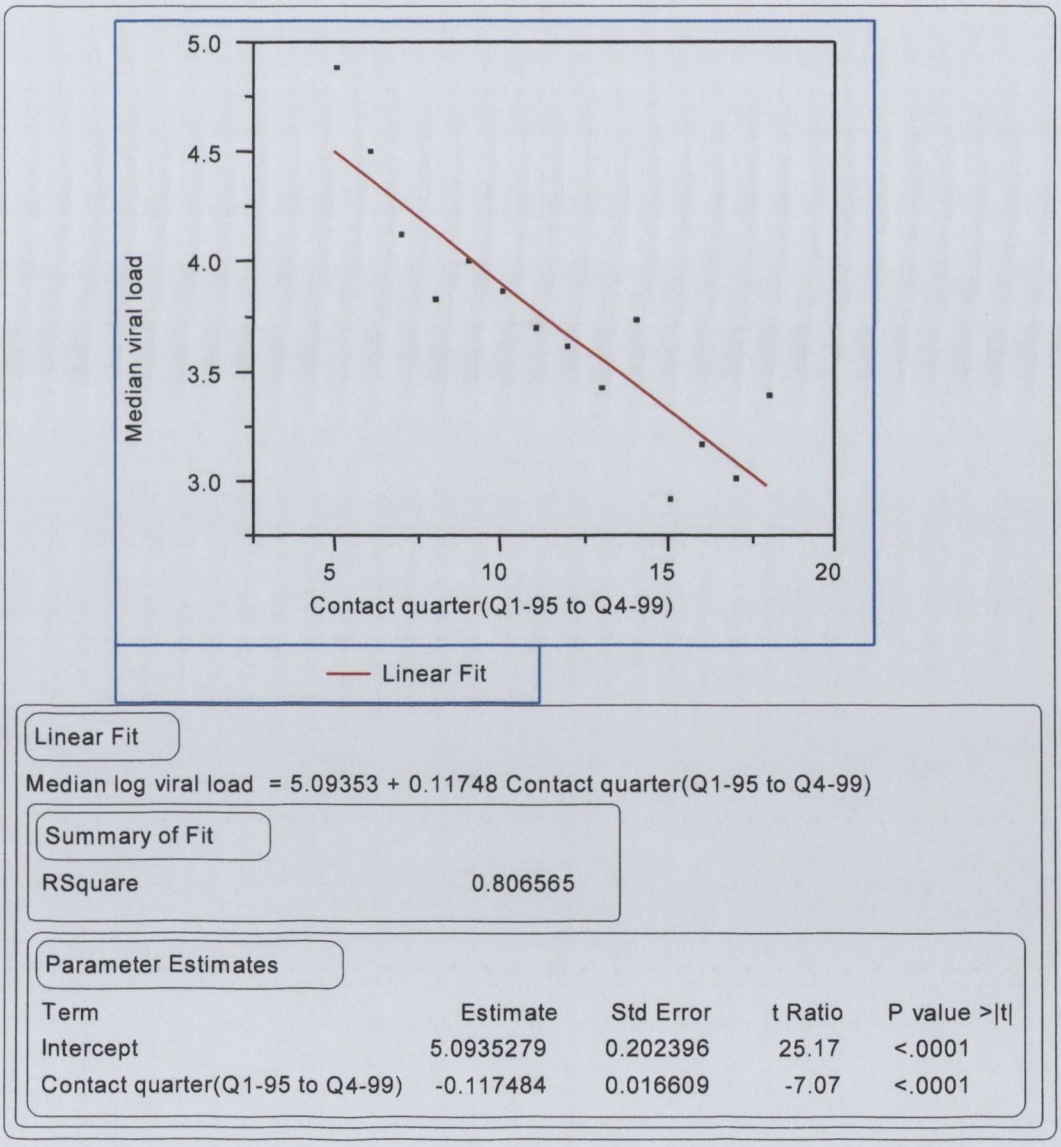


Figure 2.2 The change in median log plasma viral RNA from the third quartile of 1996 to the second quartile of 1999 inclusive.

2.4.5 AIDS defining illnesses & progression events

Details of AIDS defining illnesses and progression events are summarised in Table 2.5. The rate of diagnosis of AIDS defining illnesses declined markedly from 46.1 per 100 patient years in 1995 to 24.4 per 100 patient years during the following year, continuing to decrease steadily over the rest of the study period. There was an overall decrease in the incidence rate of respiratory tract infection, toxoplasmosis, *Mycobacterium avium* complex (MAC), Cytomegalovirus (CMV), pulmonary *Mycobacterium Tuberculosis* (TB), lymphoma, *Pneumocystis carinii* pneumonia (PCP), oesophageal candidiasis and HIV dementia. Recurrent respiratory tract infection, accounting for almost 20% of diagnoses, was the most common new AIDS defining illness diagnosed each year. In 1995, the other most common AIDS defining illnesses were MAC (12.8%), oesophageal candidiasis (15.5%) and HIV dementia (10.8%). By 1999^{proj} the most common AIDS defining illnesses besides respiratory tract infection were MAC (10%), PCP (10.5%), and lymphoma, pulmonary TB and oesophageal candidiasis which each accounted for 7.9% of all AIDS defining illnesses during that time period. The progression event rate, which includes progression to the next stage of HIV disease, all other new AIDS defining illnesses and death, declined each year from 1995 to 1998 but then increased again in 1999^{proj} to 1997 levels.

2.4.6 Hospitalisation

The absolute number of admissions each year fell somewhat in the first three years of the study from 296 admissions in 1995 to 248 admissions in 1997. It then increased again to 258 in 1998 and 131 in the first 6 months 1999 (262 admissions in 1999^{proj}). However, the admission rate for the active cohort declined steadily over the study period from 92.2 per 100 patient years in 1995 to 51.2 per 100 patient years in 1999^{proj}. The number of inpatient

Table 2.5 AIDS defining illnesses and progression rate of the active cohort.

	1995	1996	1997	1998	1999*
Number of progression events per year:	303	163	135	86	70
Rate of progression events per 100 active patient years:	94.4	43.2	32.1	18.7	27.3
Number of AIDS defining illnesses per year:	148	92	88	67	38
Rate of AIDS defining illnesses per 100 active patient years:	46.1	24.4	20.9	14.6	14.8
Most common AIDS defining illnesses rate per 100 active patient years (percentage of all AIDS defining illnesses that year):					
Respiratory tract infection	8.4 (18.2%)	4.8 (19.6%)	4.3 (20.5%)	3.5 (23.9%)	2.7 (18.4%)
Toxoplasmosis	2.5 (5.4%)	2.4 (9.8%)	1.4 (6.8%)	0.9 (6.0%)	0 (0%)
MAC	5.9 (12.8%)	2.4 (9.8%)	1.9 (9.1%)	0.4 (3.0%)	1.6 (10.5%)
CMV	3.4 (7.4%)	0.3 (1.1%)	1.2 (5.7%)	0.4 (3.0%)	0.8 (5.3%)
Lymphoma	2.2 (4.7%)	1.6 (6.5%)	1.2 (5.7%)	1.1 (7.5%)	1.2 (7.9%)
PCP	2.5 (5.5%)	2.7 (10.9%)	2.1 (10.2%)	2.2 (14.9%)	1.6 (10.5%)
Oesophageal candidiasis	7.2 (15.5%)	4.2 (17.4%)	2.4 (11.4%)	1.7 (11.9%)	1.2 (7.9%)
HIV dementia	5.0 (10.8%)	2.4 (9.8%)	1.0 (4.5%)	0.7 (4.5%)	0.4 (2.6%)
Pulmonary TB	1.9 (4.1%)	1.1 (4.3%)	0.5 (2.3%)	1.5 (10.4%)	1.2 (7.9%)
Other AIDS defining illnesses	7.2 (15.6%)	2.7 (10.8%)	5.0 (23.8%)	2.2 (14.9%)	4.3 (29.0%)

1999*: data for first 2 quartiles of 1999 only.

days fell over the first three years of the study from 2669 days in 1995 to 2297 days in 1997 but increased in 1998 to 2443 and in the first six months of 1999 to 1672 days (3344 days 1999^{proj}). The number of inpatient days per 100 patient years declined steadily from 1995 to 1998, but then increased in 1999^{proj}. Mean length of stay increased over the study period, with the greatest increase occurring in 1999^{proj}.

Demographic details of patients admitted each year are summarised in Table 2.6. Over the study period the percentage of patients admitted who were female increased from 22.6% to 35.1%. Although the admission rate amongst both females and males decreased over time, the admission rate amongst females was always greater than the admission rate amongst men. The heterosexual transmission group accounted for an increasing proportion of admissions over time. The majority of patients admitted each year were intravenous drug users. Between approximately 20% and 30% of patients admitted each year were homosexual men. The admission rate of all transmission groups fell over time except the haemophiliac cohort, which increased from 23 admissions per 100 patient years in 1995 to 40.7 per 100 patient years in 1999^{proj}. The proportion of patients admitted who had advanced to stage C disease increased from 77.4% in 1995 to 87.8% in 1999^{proj}. In parallel, the proportion with stage B disease declined over time, whereas the proportion with stage A disease accounted for between only 5-8% of all admissions during the study period. The admission rate amongst patients with stage C and stage A disease almost halved over the study period. The admission rate for patients in stage B disease decreased by almost 75%.

Approximately 70-80% of admissions each year were for HIV-related indications. The admission rate for both HIV-related and non HIV-related causes fell by almost 50% over time. The discharge diagnoses for all HIV-related admissions during the study period are summarised in Table 2.7. A number of interesting trends occurred. Management of AIDS defining respiratory tract infection accounted for the largest proportion of admissions each year except during the first year of the study. In 1995, the most common discharge

Table 2.6 Details of active cohort hospital admissions.

	1995	1996	1997	1998	1999*
Hospital admissions:	296	286	248	258	131
(rate per 100 active patient years)	(92.2)	(75.8)	(59.0)	(56.1)	(51.2)
Number of inpatient days:	2669	2560	2297	2443	1672
(rate per 100 active patient years)	(831.5)	(678.6)	(546.6)	(531.1)	(653.1)
Mean length of stay (days):	9.0	8.9	9.3	9.5	12.8
Gender:					
rate per 100 active patient years (percentage of all admissions)					
Male	88.7 (77.4%)	72.4 (74.5%)	57.8 (74.2%)	52.4 (69.2%)	46.1 (64.9%)
Female	99.6 (22.6%)	86.4 (25.5%)	64.0 (25.8%)	65.3 (30.8%)	64.1 (35.1%)
Transmission category:					
rate per 100 active patient years (percentage of all admissions)					
Homosexual	90.0 (28.5%)	76.4 (28.4%)	51.7 (26.1%)	40.3 (22.2%)	37.2 (22.1%)
Intravenous drug use	103.1 (62.3%)	80.4 (55.1%)	72.2 (54.2%)	79.8 (58.8%)	70.1 (57.2%)
Heterosexual	0.2 (7.2%)	0.2 (10.9%)	0.1 (11.3%)	0.1 (10.1%)	0.1 (15.3%)
Haemophiliac	23.0 (1.7%)	37.3 (3.9%)	42.4 (6.4%)	51.4 (7.0%)	40.7 (4.6%)
Other	0.2 (0.3%)	0.4 (1.7%)	0.2 (2.0%)	0.1 (1.9%)	0.1 (0.8%)
Stage of HIV disease:					
rate per 100 active patient years (percentage of all admissions)					
Stage A	27.3 (7.2%)	18.0 (5.6%)	13.3 (4.8%)	20.1 (8.2%)	14.8 (6.9%)
Stage B	48.0 (15.4%)	48.4 (15.8%)	29.1 (10.4%)	24.6 (8.5%)	12.4 (5.3%)
Stage C	150.7 (77.4%)	115.0 (78.6%)	87.7 (84.8%)	80.4 (83.3%)	77.8 (87.8%)

1999*: data for first 2 quartiles of 1999 only.

Table 2.7 Details of HIV-related hospital admissions.

	1995	1996	1997	1998	1999*
Number of HIV related admissions:	230	220	191	178	105
Rate of HIV related admissions per 100 active patient years:	71.7	58.3	45.4	38.7	41.0
(percentage of all admissions)	(78.8%)	(77.2%)	(76.7%)	(69.3%)	(80.2%)
Rate of specific HIV related discharge diagnoses per 100 active patient years (percentage of all HIV related admissions):					
Respiratory tract infection	15.0 (20.9%)	14.3 (24.5%)	8.1 (17.8%)	10.4 (27.0%)	10.5 (25.7%)
Infection other than AIDS defining	15.9 (22.2%)	8.2 (14.1%)	6.9 (15.2%)	6.3 (16.3%)	6.6 (16.2%)
Candidiasis	3.7 (5.2%)	3.2 (5.5%)	2.4 (5.2%)	2.4 (6.2%)	1.2 (2.9%)
CMV	5.3 (7.4%)	1.9 (3.2%)	1.0 (2.1%)	0.7 (1.7%)	0.8 (1.9%)
MAC	5.0 (7.0%)	1.9 (3.2%)	1.9 (4.2%)	0.4 (1.1%)	0.4 (1.0%)
HIV dementia	3.7 (5.2%)	1.9 (3.2%)	1.0 (2.1%)	0.2 (0.6%)	0 (0%)
PCP	2.2 (3.0%)	2.7 (4.5%)	1.0 (2.1%)	2.0 (5.1%)	1.2 (2.9%)
Toxoplasmosis	2.8 (3.9%)	4.5 (7.7%)	3.3 (7.3%)	2.2 (5.6%)	0 (0%)
HIV bone marrow suppression	2.5 (3.5%)	2.1 (3.6%)	2.1 (4.7%)	1.1 (2.8%)	0 (0%)
HIV wasting syndrome	1.6 (2.2%)	0.3 (0.5%)	1.0 (2.1%)	0.2 (0.6%)	0.8 (1.9%)
Lymphoma	5.9 (8.3%)	9.0 (15.5%)	8.1 (17.8%)	4.6 (11.8%)	9.4 (22.9%)
Cryptococcal meningitis	0.3 (0.4%)	0.3 (0.5%)	0.5 (1.0%)	0.7 (1.7%)	2.7 (6.7%)
Cryptosporidia	0.6 (0.9%)	0.5 (0.9%)	0.2 (0.5%)	0.4 (1.1%)	0 (0%)
Pulmonary TB	1.2 (1.7%)	1.9 (3.2%)	0.7 (1.6%)	1.5 (3.9%)	1.2 (2.9%)
Adverse drug reaction	3.7 (5.2%)	2.9 (5.0%)	3.6 (7.9%)	4.3 (11.2%)	3.9 (9.5%)
Other	(3.0%)	(4.9%)	(8.4%)	(3.3%)	(5.5%)

1999*: data for first 2 quartiles of 1999 only.

diagnosis was non-AIDS defining infection. The proportion of admissions attributed to HIV-related lymphoma, which was 8.3% in 1995, was greater in all subsequent years peaking at 22.9% in 1999*. Percentages of admissions due to CMV, MAC infections and HIV dementia declined over time. Admissions due to PCP and candidiasis peaked in 1998, while the proportion due to toxoplasmosis peaked in 1996. Cryptococcus meningitis accounted for 6.7% of admissions in 1999* but for only a small proportion of admissions during each other year of the study. Interestingly, there was an overall increase in the proportion of admissions for management of adverse drug reactions peaking at 11.2% in 1998. Similarly, trends in admission rates associated with different discharge diagnoses were noted. The rate of admission of recurrent respiratory tract infection declined each year from 15 per 100 patient years in 1995 to 10.5 per 100 patient years in 1999*. The rate of admission due to non-AIDS defining infection also decreased over time. The rates of admission due to MAC, candidiasis, CMV, cryptosporidia, HIV induced bone marrow suppression, HIV dementia complex, and wasting syndrome declined over the study period. Rates of admission for toxoplasmosis and PCP varied. There was an overall increase in the admission rate associated with HIV-related lymphoma, cryptococcal meningitis and for management of adverse drug reactions.

Details of non HIV-related admissions during the study period are summarised in Table 2.8. Between 30 – 50% of non HIV-related admissions each year were directly associated with intravenous drug use including discharge diagnoses such as deep vein thromboses, accidental overdose etc.. Hepatitis B and hepatitis C resulted in between 5 – 9% of admissions each year except 1999* when infective hepatitis accounted for 19.6% of all non-HIV related admissions. Admission of haemophiliacs for management of haemorrhages under the haematology team accounted for between approximately 5% to 25% of non HIV-related admissions.

Table 2.8 Details of non HIV-related hospital admissions.

	1995	1996	1997	1998	1999*
Number of non-HIV related admissions:	62	65	58	79	26
Rate of non-HIV related admissions per 100 active patient years:	19.3	17.2	13.8	17.2	10.2
(percentage of all admissions)	(21.2%)	(22.8%)	(23.3%)	(30.7%)	(19.8%)
Rate of specific non-HIV related discharge diagnoses per 100 active patient years (percentage of all non-HIV related admissions):					
Bleeding in haemophiliacs	19.3 (4.8%)	17.2 (15.4%)	13.8 (22.4%)	17.2 (17.7%)	10.2 (7.7%)
Hepatitis B or C	3.4 (8.1%)	2.7 (7.7%)	1.4 (8.6%)	2.6 (5.1%)	2.0 (0%)
Intravenous drug use related	7.5 (38.7%)	7.7 (44.6%)	7.1 (51.7%)	5.2 (30.4%)	3.5 (34.6%)
Other	(48.4%)	(32.3%)	(17.3%)	(46.8%)	(57.7%)

1999*: data for first 2 quartiles of 1999 only.

2.4.7 Outpatient contacts

The total number of outpatient contacts increased each year from 2634 in 1995 to 3994 1999 ^{proj} but the number of outpatient contacts per active patient in the cohort fell over the study period.

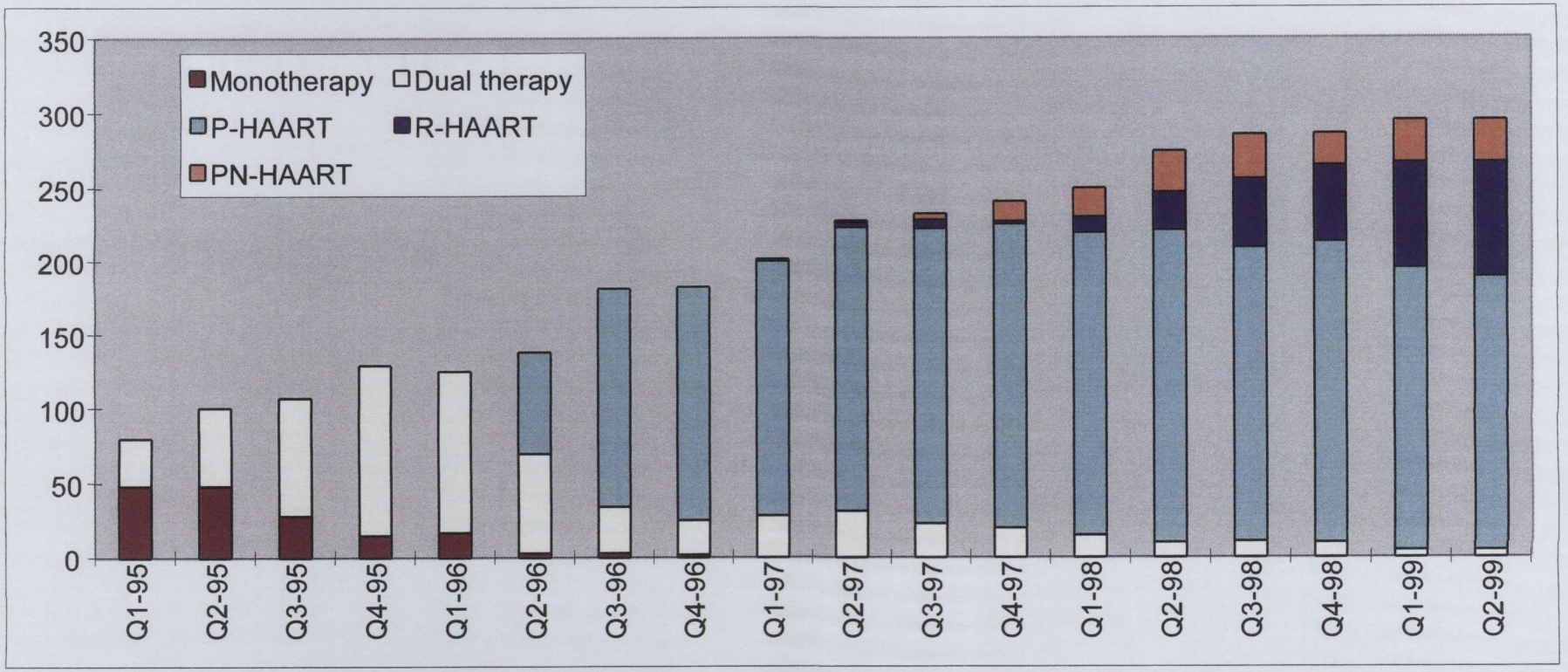
Table 2.9 Outpatient contacts of the active cohort.

	1995	1996	1997	1998	1999*
Number of outpatient contacts:	2634	2757	2984	3418	1997
Rate of outpatient contacts per 100 active patient years:	821	731	710	743	780

2.4.8 Antiretroviral therapy

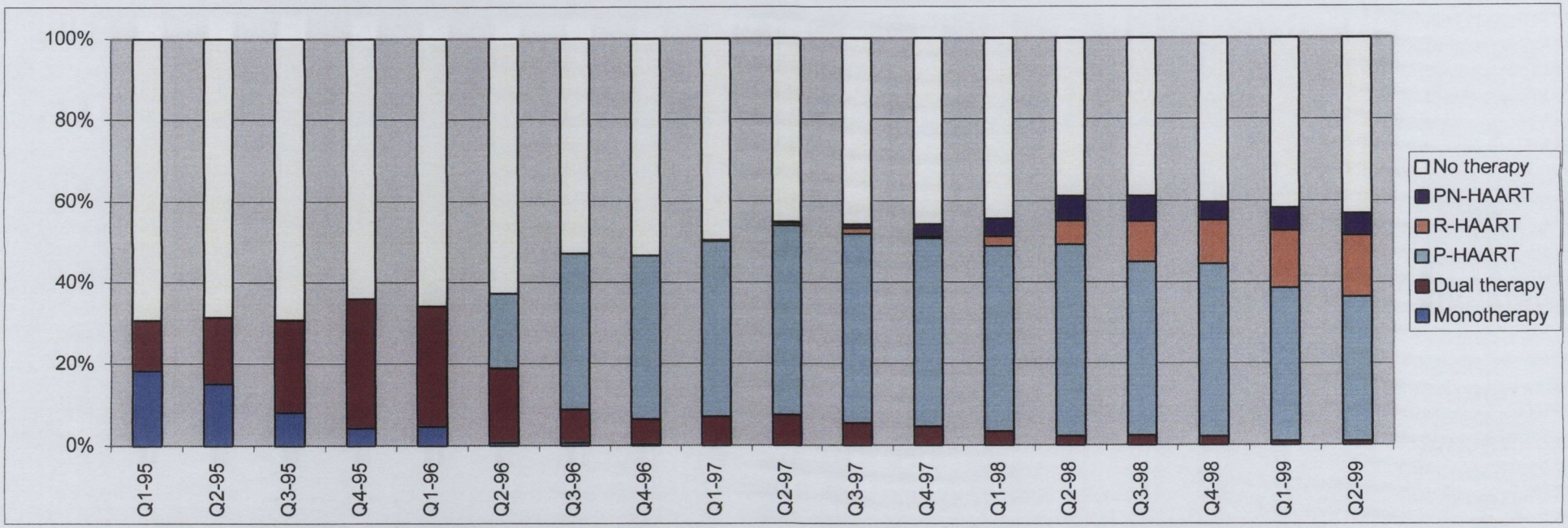
The number of patients prescribed anti-retroviral therapy each quartile increased almost four fold over the study period from 80 patients in the first quarter of 1995 to 295 patients in the last quartile (Figure 2.3). The proportion of the active cohort who received treatment almost doubled, increasing from 31% at study onset to 57% at study closure (Figure 2.4).

No patient received single agent antiretroviral therapy after 1996. From the second quarter of 1995 until the second quarter of 1996 when the protease inhibitors became available the majority of patients treated received two anti-retroviral agents. After the second quartile of 1996, dual therapy was prescribed to a minority of treated patients. Over this period, the majority of patients on antiretroviral therapy received HAART. All patients prescribed HAART, received regimens containing a protease inhibitor from the second quartile of 1996 to the first quartile of 1997 inclusive. From the second quartile of 1997 on, the proportion of those on HAART who were prescribed a protease inhibitor fell consistently to 73% at the end of the study period. Conversely there was an increase in the prescribing



Note: P-HAART: HAART containing protease inhibitor, R HAART containing reverse transcriptase inhibitors only, PN HAART containing protease inhibitors plus non-nuceoside reverse transcriptase inhibitor.

Figure 2.3 Frequency of prescribing antiretroviral regimens to patients in the active cohort each quartile from the first quartile of 1995 to the second quartile of 1999 inclusive.



Note: **P-HAART: HAART containing protease inhibitor, R HAART containing reverse transcriptase inhibitors only, PN HAART containing protease inhibitors plus non-nuceoside reverse transcriptase inhibitor.**

Figure 2.4 Frequency of prescribing antiretroviral regimens as a proportion of the active cohort each quartile from the first quartile of 1995 to the second quartile of 1999 inclusive.

of HAART regimens, which included a non-nucleoside reverse transcriptase inhibitor. Diffusion of HAART through the active cohort coincided with a substantial increase in the median CD4 cell count from baseline and a substantial decrease in mortality rate (Figures 2.5, 2.6).

2.5 Discussion

Intensification of antiretroviral therapy strategies over the study period has coincided with changes in surrogate markers of disease progression and clinical end point data including mortality, disease progression, AIDS defining illnesses and hospitalisations.

2.5.1 Active cohort & new attendee demographics

The overall increase in the number of new patients registering with the service each year together with a decline in mortality rate contributed to an almost two fold increase in the size of the active cohort over the four and half year period under review. The statistically significant increase in the proportion of new attendees who were female together with a much lower mortality rate amongst women from 1996 on resulted in a statistically significant increase in the number of female members in the active cohort. The increase in the female proportion of the active cohort was paralleled by an increase in the proportion presumed to have acquired HIV through heterosexual contact. The greater number of heterosexual patients attending may be explained by the launch of a national ante-natal screening program in 1998 and an overall increase in the number of African patients for whom the predominant mode of transmission is heterosexual [9]. The increased number of African patients reflects the increased influx of asylum seekers into Ireland in the last few years from countries in sub-Saharan Africa where HIV is endemic.

Although the proportion of intravenous drug users declined over the study period, there was a sharp increase in the proportion of new attendees from this risk group in 1999*. The

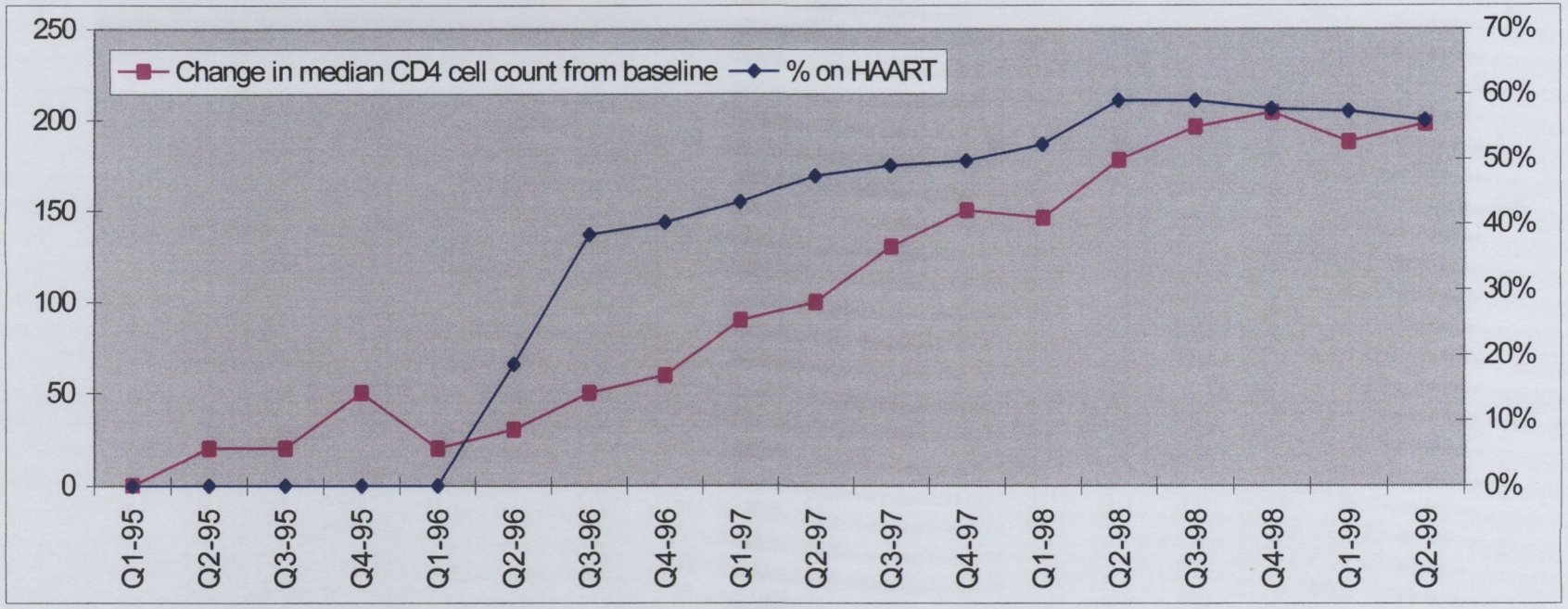


Figure 2.5 The change in median CD4 cell count of the active cohort from baseline and the percentage of the active cohort prescribed HAART each quartile from the first quartile of 1995 to the second quartile of 1999 inclusive.

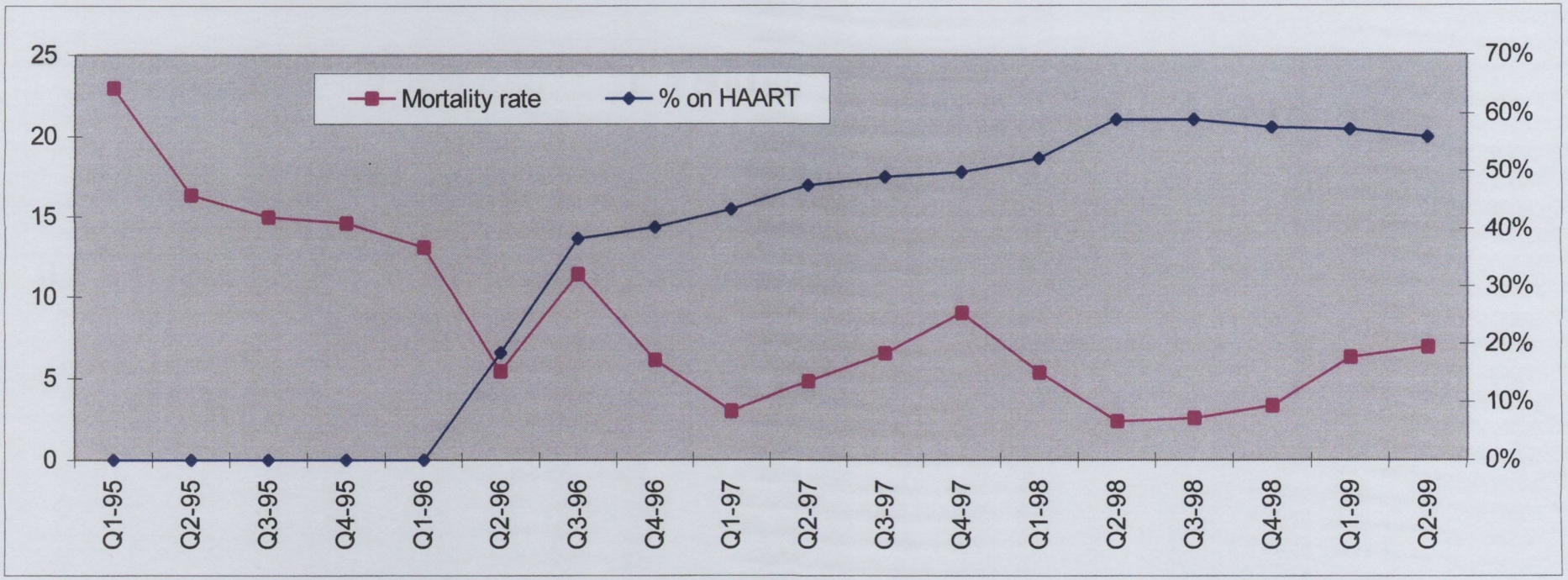


Figure 2.6 **Mortality rate per 100 active patient years and the percentage of the active cohort prescribed HAART each quartile from the first quartile of 1995 to the second quartile of 1999 inclusive.**

centralisation of methadone dispensing in the city in the latter half of 1998 and resultant increased testing for HIV amongst the drug using community may have contributed to this finding [9]. Towards the end of 1998, a cluster of new diagnoses from one geographical location within the city was identified [9]. This group consisted of intravenous drug users, the majority of whom were under 25 years, who were engaging in needle sharing and unprotected sexual intercourse. Another initiative which may have contributed to the increase in the number of new attendees in the latter part of the study period was a decision in 1998 to introduce routine HIV testing for all patients who attended the sexually transmitted diseases clinic at our centre. The number of new attendees who were haemophiliac peaked in 1996 when a decision was taken by the National Haemophilia Centre to transfer the majority of their HIV-infected haemophiliacs to our clinic for management of their HIV disease. This move coincided with the availability of HAART in this country and recognition that patient benefit derived from these potent albeit complex regimens could be maximised in a specialist setting. Besides the increase in the proportion of African born participants in the cohort, there was also an overall increase in the proportion born in the UK and in other countries outside the EC not including Africa. These trends may be explained by greater mobility within the international community and may have been influenced to some extent by the restrictions on prescribing HAART in the UK and some other countries including South America and Mexico [51]. The net result was a decrease in the Irish born proportion of the active cohort.

2.5.2 CDC Stage of HIV disease

The proportion of new attendees in stage A disease peaked in 1999* coinciding with identification of the cluster of young intravenous drug users in the community at the end of 1998 and increased emphasis on testing of this transmission risk group. The proportion of the active cohort in stage C disease increased over time corresponding to a decrease in proportion with stage B disease over the same time period. This finding may be attributed to the impact of more potent antiretroviral therapy in arresting disease progression from

diagnosis of stage C disease to death resulting in accrual of patients in the most advanced stage of disease over time. In 1995 and the first and second quartiles of 1996, only patients already advanced to stage C disease were eligible for antiretroviral therapy. From the third quartile of 1996, the criteria for initiation of antiretroviral therapy was extended to include patients in stage B with CD4 cell counts <500 x 10^6/ml and plasma viral RNA >10,000 copies per ml. However, the main benefit of antiretroviral therapy in terms of decreased mortality was evident in the stage C group thus explaining the increased proportion of patients with stage C disease over time.

2.5.3 Mortality

Mortality rate decreased by almost five fold from 16.8 in 1995 to 3.5 per 100 active patient years in 1998 temporally coincident with intensification of antiretroviral strategies including expansion of treatment criteria and adoption of HAART as standard of care (Figure 2.6). This changing pattern of mortality was similar to that reported by the EuroSIDA cohort (a pan-European study of patients infected with HIV-1 attending 50 centres throughout Europe)[49]. In EuroSIDA, death rate declined from 23.3 per 100 person-years between March and September 1995 to 4.1 per 100 person years of follow-up between September 1997 and March 1998. In our cohort, mortality rate was higher amongst male participants. Similarly the mortality rate amongst intravenous drug users and homosexuals exceeded the heterosexual mortality rate. The Swiss HIV cohort and the John's Hopkins cohort previously reported no difference in risk of progression to AIDS or death between men and women or amongst patients with or without a history of intravenous drug use [52, 53]. The increased crude mortality rate observed amongst homosexuals and intravenous drug users in our study is most likely due to increased duration of infection in these subgroups as suggested by their relatively greater age and lower CD4 cell counts (data not shown). Both of these characteristics have been reported to correlate with risk of progression to AIDS and death.

There was an upturn in mortality rate in the first 6 months of 1999 to 6.6 per 100 active patient years. However clinical end point data for 1999 may be subject to modification pending analysis of data for the latter half of the year. Alternatively, the upturn in mortality may indicate that the therapeutic benefit of HAART in patients, who were in the penultimate stage of HIV disease when HAART became available, may now have become exhausted. Ongoing monitoring of clinical endpoint data is required to interpret the significance of this chapter's findings.

2.5.4 Immunology & Virology

The CD4 cell count is recognised as a surrogate marker of the extent of HIV-related destruction of the immune system and an independent predictor of progression of HIV disease [27]. The frequency and severity of clinical manifestations of HIV disease increase with decline in CD4 cell count [54]. Therefore the statistically significant increase in the median CD4 cell count over the study period reflects an improvement in the overall immune status of the cohort over time ($p<0.0001$, $R^2 = 0.948$, median CD4 = 95.7 + 13.3contact quarter). The increase in median CD4 cell count from baseline occurred temporally coincident with intensification of antiretroviral strategies and increased uptake of HAART amongst the active cohort (Figure 2.6).

A CD4 cell count of 200 x 10^6/L is considered the threshold below which there is a greatly increased risk of opportunistic infection [55-57]. The increase in the proportion of patients with CD4 cell counts between 201 – 500 and > 500 x 10^6/L over time observed in this study may represent an increase in the immunocompetency of the cohort and subsequent decreased risk of opportunistic infections [54]. For a number of conditions there is an increased risk of infection when CD4 cell count is less than 50 - 75 x 10^6/L, for example MAC, CMV [55]. The proportion of patients with CD4 cell counts between 51 and 100 x

10^6/L and less than 50 x 10^6/L decreased over the study period suggesting a reduction in the risk of these late stage indicative infections. Mortality rate has been shown to increase as the CD4 cell count approaches zero [55]. Therefore, the decrease in the proportion with CD4 cell counts < 50 x 10^6/L is consistent with reduced mortality rates observed in this cohort. Recovery of the CD4 cell count subsequent to the introduction of antiretroviral therapy has been associated with improvement in clinical progression rates [58].

Plasma viral RNA is recognised as a surrogate marker of HIV disease activity and the level of response to antiretroviral therapy [24, 27]. There was a statistically significant decline in the median log viral load over the study period ($p<0.0001$, $R^2 = 0.806$, median log viral load = 5.09 + 0.12 contact quarter). In addition, the proportion of patients with viral load < 400 copies per ml and the proportion with viral loads below the limit of detection of the assay at the time of testing increased over the study period. This pattern of enhanced viral suppression noted over time may have translated into substantial benefit in terms of clinical endpoints including decreased HIV disease progression rate and decreased mortality rate as a consequence of better response to antiretroviral therapy. This interpretation is supported by other studies that have demonstrated a treatment-related change in surrogate markers to be predictive of clinical benefit [58, 59].

2.5.5 AIDS defining illnesses & progression events

The rate of diagnosis of AIDS defining illnesses decreased by 68% over the study time from 46.1 in 1995 to 14.8 per 100 active patient years in 1999^{proj} representing a substantial improvement in morbidity previously associated with HIV infection. Criteria for initiating prophylaxis against PCP pneumonia, MAC and toxoplasmosis remained unchanged over the study period. A decrease in the incidence of AIDS defining illnesses coincident with intensification of antiretroviral therapy has been noted in other centres [46, 60, 61]. Brodt et al demonstrated a 70% decrease in the incidence of AIDS defining illnesses in patients

with a CD4 cell count less than 200 x 10^6/L between 1992 and 1996 coincident with a shift from monotherapy, to combination therapy, to HAART as the predominant antiretroviral strategy [61]. The Swiss cohort study also noted a substantial decrease in the combined incidence of AIDS related opportunistic illnesses in 2410 HIV-infected patients subsequent to initiation of potent protease inhibitor containing regimens [46]. The Swiss study reported much lower incidence rates of opportunistic illnesses before and within fifteen months after the introduction of protease inhibitor containing therapy than those observed in our cohort, (15.1 per 100 person years and 3.57 per 100 person years of follow-up respectively). However this difference in incidence rate of opportunistic infections may be explained by differences in study design between the Swiss cohort study and our study. The Swiss study included only those patients initiated on protease inhibitors, whereas we examined the incidence rate of opportunistic illnesses in the entire cohort, noting that only a proportion of patients were prescribed antiretroviral therapy i.e. up to 60%. The EuroSIDA study recently reported a decline in the incidence of AIDS defining illnesses from 30.7 per 100 patient years in 1994 to 2.5 per 100 patient years in 1998 [60]. The lower rates of AIDS defining illnesses reported by EuroSIDA compared to rates noted in this chapter may also be explained by differences in study design. Our definition of the active cohort is more stringent than EuroSIDA where lost to follow-up was defined as no clinical follow-up within the last calendar year [49]. The resultant increase in the relative size of the active cohort would result in lower incidence rates for clinical events. The rate of occurrence of AIDS indicative infection has been shown to be predictive of risk of death [62]. In our study falling incidence of AIDS defining illnesses mirrored declining mortality rate.

Recurrent respiratory tract infection was the most common new AIDS defining illness diagnosed and accounted for a similar proportion of all new AIDS defining illnesses each year. There was an overall decrease in the proportion of new diagnoses of CMV and MAC consistent with an increased proportion of the cohort with CD4 cell counts in excess of 100

x 10^6/L. EuroSIDA reported similar trends [60]. The incidence of HIV dementia complex, which was amongst the most frequently diagnosed AIDS defining illnesses in 1995, reduced substantially over the period under review. The incidence of lymphoma in our cohort changed little similar to the pattern observed in the Swiss cohort study [63], but accounted for an increasing proportion of all new diagnoses and therefore accounted for an increasing proportion of admissions over time.

Progression events were defined to include new stage B diagnoses, new stage C diagnoses, subsequent diagnoses of AIDS defining illnesses for the first time and deaths. The progression event rate decreased over the study period reflecting an overall increase in the well being of the cohort.

2.5.6 Hospitalisation

There was an overall decrease in the absolute number of hospital admissions over time corresponding to a more marked decrease in the admission rate per 100 active patient years since the denominator had almost doubled over the study period. This decrease in admission rate observed following the introduction of HAART accords with the findings of other investigators [48, 64]. Ten year data up to 1997 from the Royal Free cohort (n=1806) reported a consistent decline in admission rates [65]. The observed trend was attributed to intensification of antiretroviral therapy, increased experience in treating the disease, the introduction of new therapies for specific opportunistic illnesses and the increased use of prophylaxis against PCP pneumonia. In our study, the number of inpatient days decreased over the first 4 years of the study in line with the number of admissions but increased in 1999* because of the substantial increase in mean length of stay during that time period.

There was an overall increase in the proportion of patients admitted who were female thus reflecting the changing demographics of the active cohort over the study period. It was also

noted that the admission rate amongst females was always higher than amongst males despite the fact that the male cohort had more advanced HIV disease as a whole. Haemophiliacs constituted the only transmission group, which demonstrated an increase in admission rate over time. On more detailed analysis, this may be partly explained by the increase in the proportion of haemophiliacs in the active cohort from 1996 onwards. The majority of haemophiliac admissions were non HIV-related. Non HIV-related admissions were predominantly for management of complications of haemophilia. Of five admissions classified as HIV-related, two were due to adverse drug reactions to antiretroviral therapy. Although the admission rate of the heterosexual transmission group declined over time, this group accounted for an increasing proportion of admissions mirroring the increased proportion of the active cohort represented by this group. There was a marked decline in admission rate amongst patients in each stage of HIV disease. However, the proportion of patients admitted with stage C disease increased, which again may be explained by the overall increase in the proportion of the active cohort, which had advanced to the final stage of HIV disease.

The HIV-related admission rate almost halved over time reflecting improved status of HIV disease. The non HIV-related admission rate also fell. This may be explained by the overall decrease in the size of the intravenous drug using proportion of the cohort who were responsible for the majority of non HIV-related admissions each year. AIDS defining respiratory tract infection and infection other than AIDS defining were the most frequent HIV-related discharge diagnoses. The admission rate associated with these indications and with most other HIV-related diagnoses fell over time reflecting a better state of health of the active cohort. However, the admission rate due to HIV-related malignancy increased. This occurred despite no overall increase in the incidence of lymphoma in the cohort. One explanation is that combining standard chemotherapy with HAART has resulted in prolonged survival amongst lymphoma patients post diagnosis compared to the pre-HAART era and subsequently increased hospitalisation. There was an increase in

admission rate and the proportion of admissions due to adverse drug reactions subsequent to the introduction of HAART. Specific reasons for admissions in this category included drug-induced hepatitis, nephrolithiasis associated with indinavir and management of rash in patients prescribed nevirapine or abacavir. Therefore, although intensification of antiretroviral strategies has resulted in profound improvements in disease progression and mortality, these agents are associated with a considerable degree of iatrogenic morbidity.

A substantial increase in mean length of stay was observed in the last six months of the study. This may be explained by closer analysis of the case-mix. Lymphoma and cryptococcal meningitis accounted for a much larger proportion of admissions in the first 6 months of 1999 than during the remainder of the period under review. These indications are associated with relatively prolonged duration of hospitalisation and therefore inflated the mean length of stay.

2.5.7 Outpatient contacts

Although an increase in the absolute number of outpatient contacts occurred over the study period, the number of outpatient contacts per active patient in the cohort changed little. Torres and Barr reported an observed decrease in inpatient admissions and a coincident increase in outpatient contacts subsequent to adoption of HAART [66]. In our cohort, a decrease in admission rate and the number of inpatient days per active patient in the cohort has occurred without an increase in outpatient contact.

2.5.8 Antiretroviral therapy

There was a marked increase in the number of patients receiving antiretroviral therapy over the study period due to a number of factors. As described in chapter 1, in the third quartile of 1996, the "Hit Early, Hit Hard" treatment strategy was adopted which resulted in

initiation of therapy much earlier in the course of HIV disease and therefore a substantial increase in the number of patients eligible for treatment. However, an increase in numbers treated occurred before this paradigm shift in 1996 as a result of the increased number of patients in the active cohort every quartile of the study period. Decreased mortality, which was evident from the beginning of the study, resulted in an overall increase in the numbers eligible for treatment each quartile. Patients with more advanced disease who were most likely to be receiving antiretroviral therapy exhibited the greatest reduction in mortality rate, thereby further augmenting the size of the treated cohort. This translated into a twofold increase in the proportion of the active cohort that received antiretroviral therapy.

As explained in Chapter 1, there was a switch from single agent therapy to dual combination therapy over the first five quartiles subsequent to publication of the results of the ACTG study 175 and the Delta study which, advocated dual therapy and coincident with the availability of lamivudine through an expanded access program [19, 20]. With the availability of the protease inhibitors in the second quartile of 1996, a switch to HAART initially including nucleoside reverse transcriptase inhibitors plus one or more protease inhibitors quickly took effect. The non-nucleoside reverse transcriptase inhibitors became available in the first quartile of 1997 and were subsequently incorporated into alternative HAART regimens combined either with nucleoside reverse transcriptase inhibitors or in combinations with nucleoside reverse transcriptase inhibitors and protease inhibitors. Selection of the components of a HAART regimen was individualised to the patient taking consideration of such factors as previous exposure and likely resistance profile of the virus, disease status, tolerability profile, interacting medication, complexity of administration schedule and patient preference [67].

When HAART was adopted as standard of care in 1996, evidence to support this policy relied on surrogate marker data from early clinical trials [43, 44, 68]. However clinical end point data from clinical trials and observational data from other countries where these

drugs had been available earlier than in Ireland soon confirmed the superior antiviral efficacy of HAART over previous strategies [12, 46, 69]. In Ireland, a minority of patients continued to receive only two antiretroviral agents. Indications for dual therapy included inability of the patient to manage a more complex regimen, an initial reluctance to prescribe protease inhibitors to haemophiliacs who were resistant to clotting factor replacement therapy and in the case of pregnancy to prevent transmission of HIV to the baby when the mother's own disease status would not warrant antiretroviral intervention.

As mentioned earlier the threshold CD4 cell count for initiation of antiretroviral therapy was 200 x 10^6/L during the first six quartiles increasing to 500 x 10^6/L for the rest of the study period. On closer analysis, the percentage of patients with CD4 cell counts below the stated threshold was consistently greater than the percentage on antiretroviral therapy. However the proportion of patients with counts below the threshold may be an over estimation since this value reflects only patients who have had a CD4 cell count measurement during that quartile. Patients with CD4 cell counts above the threshold are less likely to attend clinic every quartile and therefore to contribute to the CD4 cell profile to the same extent as those with a considerable degree of immunosuppression for whom antiretroviral therapy is indicated. Patients who fulfil the disease criteria for initiation of therapy may not receive it for a number of reasons including patient preference, failure to comply with previous antiretroviral therapy or chaotic intravenous drug use.

Substantial reduction in mortality rate, improvement in immunological and virological profiles of the cohort, reduction in the incidence of AIDS defining illnesses, decline in progression rate and reduction in hospitalisation rate occurred during the period under review while there was no change in opportunistic infection prophylaxis regimens. These changes took place coincident with an initial switch from monotherapy to dual therapy and then from dual therapy to HAART as standard of care. Although a causal link between improved health status for this cohort and intensification of antiretroviral therapy strategies

cannot be implied from purely observational studies, introduction of more potent regimens as standard of care is the most likely explanation for the improvements noted.

Another factor, which may have contributed to improved prognosis of the cohort albeit to a lesser extent than the increased potency of antiretroviral therapy was the availability of viral load testing in 1996. Viral load measurement facilitates more accurate evaluation of disease status and interpretation of response to antiretroviral therapy than previously possible with CD4 cell count alone [24]. Also, this patient group was under the supervision of a single specialist for the study period. Increased experience of the treating physician has previously been demonstrated to impact positively on patient's outcomes [70]. No other factors have been identified to contribute to the improved well being of these patients over the time period under review.

Changes in demographic trends of the active cohort over time have important consequences for planning of service provision and the focus of education and testing. There is increased awareness of the special needs of female patients in particular with regard to pregnancy issues. Developments to address this issue include a joint clinic once a month with the obstetric HIV services. Following identification of a cluster of newly infected intravenous drug users as described earlier, the drug treatment services and the general practitioners in the area were informed to highlight the ongoing need for HIV testing and provision of education on safe behaviour [9]. The size of the cohort attending regularly has almost doubled with a greater proportion of these patients in the most advanced stage of disease. Nevertheless, although an overall reduction in morbidity has resulted in decreased admission rates, the number of admissions has not diminished due to the increased size of the cohort. There has been an increase in the absolute numbers of outpatient contacts (Table 2.8). The work load of the outpatient clinic is further increased by the greater proportion of patients receiving antiretroviral therapy and therefore requiring intense monitoring of efficacy and toxicity, via clinical and laboratory evaluation. Despite

an increased proportion of a larger cohort in the most advanced stage of disease, improved morbidity has translated into diminished demand for hospice home care, palliative care, counselling and dietetic services. Consequent changes in resource management have resulted in reduced hospice and dietetic input, redirection of counsellor time towards other sexually transmitted disease services provided concomitantly by the clinic and increased medical, nursing and pharmacy staff allocations.

Adopting HAART, which carries a comparatively high drug acquisition cost, as standard of care and the overall increase in the numbers treated has major implications for the pharmacy budget. The decreased incidence of new AIDS defining illnesses noted might be expected to result in an overall reduction in the cost of managing opportunistic infection. However, it is also possible that increased longevity may not result in a reduction in the number of patients receiving lifelong maintenance therapy. In the pre-HAART era, maintenance therapy for many opportunistic infections or prophylaxis therapy once the nadir CD4 cell count had declined below the specific high-risk threshold was life long. Subsequent to unprecedented immune reconstitution associated with HAART, many centres are now discontinuing maintenance or prophylaxis regimens in patients who are virologically stable and have maintained CD4 cell counts in excess of the high risk thresholds for at least six months [71-73]. This strategy further complicates drug expenditure and careful analysis is required to accurately determine trends in expenditure and to facilitate projection of future drug budget requirements.

Adoption of HAART as standard of care has implications for healthcare provided to HIV-infected individuals. Changes in disease presentation have required development of expertise in management of conditions, which have become more commonplace such as non Hodgkin's lymphoma. Decreased incidence and therefore experience of some AIDS defining illnesses and other previously common presentations, for example HIV dementia may result in deskilling of personnel in management of these indications. Safe prescribing

of HAART requires expertise in managing the substantial drug interaction profiles of the constituents and has resulted in modification of previous therapy guidelines for treating HIV-related disease to take account of these drug interactions. Adverse drug reactions now contribute substantially to the inpatient burden. Skills in minimising and managing the toxicity of the components of HAART are essential. Because of the improved prognosis of HIV disease, it is important to consider co-morbidities, which may now impact on patients' overall prognosis, for example hepatitis B and C, drug-induced hypercholesterolaemia and hypertriglyceridaemia. As a consequence, initiation of therapy for such co-morbidities is now dependent on the same criteria as for non-HIV-infected individuals [74-76].

Although clinical improvements have been demonstrated with HAART, strict adherence to what are often complex or toxic regimens is required to maximise the potential benefits. This may involve considerable interference with daily schedules to facilitate multiple daily dosing, food and fluid restrictions. Living with HIV infection since before the HAART era has required an alteration in perception of HIV from an acutely progressing disease associated with short survival despite antiretroviral intervention to a chronic illness with prospects of greatly increased survival dependent on adherence to therapy. This realisation has important implications for future personal financial requirements and means that many patients who had terminated employment have returned to work or enrolled in education or training programs with the intention of rejoining the workforce. As mentioned earlier, sustained viral suppression has, in addition to prolonging life expectancy, greatly attenuated the risk of vertical transmission, thereby making pregnancy a very real option for couples who would previously not have considered it.

2.6 Conclusion

To facilitate the evaluation of the impact of HAART in our clinic cohort, a comprehensive, observational cohort database was constructed. Analysis of the database revealed that

intensification of antiretroviral strategies including adoption of HAART as standard of care has coincided with unprecedented improvement in surrogate markers of disease progression, decline in mortality rate and reduction in morbidity as evidenced by decreased incidence of AIDS defining illnesses and reduced hospitalisation rates.

HAART represents a major milestone in slowing the natural progression of HIV disease. In this chapter, data from the first Irish observational cohort has been used to demonstrate and quantify substantial benefits associated with HAART previously identified in other settings. Adopting HAART as standard of care has resulted in a four-fold increase in drug expenditure. Characterising the cohort and quantifying the benefits associated with HAART facilitates an assessment of the pharmacoeconomic impact of these agents in this country thereby providing a benchmark against which newer strategies can be evaluated. Establishment of the observational cohort database constituted an essential resource in estimating the cost of providing inpatient and outpatient care for our cohort and subsequently determining the impact of HAART on HIV healthcare expenditure. In addition the database provided the foundation for more in depth analysis of the impact of HAART on a number of specific HIV-related opportunistic infections. The impact of HAART on the pharmacoepidemiology and pharmacoeconomics of MAC, toxoplasmosis, candidiasis and CMV retinitis will be described in the following chapters.

CHAPTER 3

3 THE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON THE PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS OF *MYCOBACTERIUM AVIUM* COMPLEX INFECTION.

3.1 Introduction

Since the onset of the HIV pandemic, a number of advances have decreased morbidity and mortality associated with opportunistic disease. Clarithromycin used as *Mycobacterium avium* complex (MAC) prophylaxis has been shown to improve survival in HIV-infected individuals [77]. The introduction of more effective treatment regimens for specific opportunistic infections has also improved prognosis. In a retrospective review of 103 infected patients, median survival from diagnosis of MAC infection increased from 168 to 284 days. Increased survival was associated with the introduction of macrolide antibiotics as standard of care therapy for MAC [78].

The most effective means of improving prognosis is prevention of HIV disease progression. By suppressing HIV replication, and maintaining or increasing CD4 cell counts above the high risk threshold for opportunistic infections (CD4 > 200 x 10^6/L) with effective antiretroviral therapy, the probability of developing opportunistic infections can be reduced substantially. A number of epidemiological studies of overall morbidity and mortality of HIV-infected cohorts have demonstrated the beneficial effects of antiretroviral therapy [12, 46, 60]. In our cohort, which includes all patients who regularly attend our service regardless of stage of disease or CD4 cell count, we have demonstrated an overall reduction in mortality of 79.3% between 1995 and 1998. Meanwhile, the incidence of AIDS defining opportunistic infection in our patient cohort has declined from 46.7 per 100 active patient years in 1995 by 68.3% to 14.8 per 100 active patient years in 1998 (Table 2.5). These changes in morbidity and mortality coincided with the intensification of antiretroviral therapy in particular the adoption of HAART as standard of care and the expansion of the criteria for initiation of antiretroviral therapy at our centre in mid-1996.

There have been a number of reports of dramatic improvements in the morbidity and mortality of HIV-infected individuals who have access to HAART. Although improved prognosis has been welcomed, the high drug acquisition cost of HAART poses considerable financial implications for health service providers. HAART is associated with a high drug acquisition cost. The annual drug acquisition cost per patient of commonly prescribed first 3-drug HAART regimens varies from IR£6,000 to IR£8,000 depending on the constituent drugs. Salvage drug regimens, which may include 4 or more drugs, are even more expensive. It is reasonable to suggest that the high drug acquisition cost of HAART might be offset to some extent by cost savings due to decreased expenditure on treatment of opportunistic infections.

3.2 Aim

The history of MAC was examined in our treatment cohort before and after the introduction of highly active antiretroviral therapy (HAART). The aim of the chapter was to measure the impact of HAART on the epidemiology, pharmacoepidemiology and pharmacoeconomics of MAC infection. To this end, the incidence of MAC infection, the survival from time of diagnosis of MAC infection, mortality, prescribing trends and cost of treatment were determined. The extent to which increased acquisition cost of antiretroviral therapy could be offset by the expected decrease in outpatient cost of managing this opportunistic infection was also investigated.

3.3 *Mycobacterium avium* complex

3.3.1 Aetiology

MAC is an indicator opportunistic disease of late stage HIV infection. MAC includes *Mycobacterium avium*, *Mycobacterium intracellulare* and some other strains not yet classified. In contrast to *Mycobacterium tuberculosis,* MAC organisms are ubiquitous in

the environment and have been recovered from fresh water, seawater, soil, dairy products and animals. MAC organisms are acid-fast bacilli but unlike *Mycobacterium tuberculosis* are not usually pathogenic to the healthy host. Acquisition of MAC is thought to be through inhalation or ingestion of organisms from the environment. There is no documentation of transmission from person to person.

3.3.2 Epidemiology

In the pre-HAART era, disseminated MAC (d-MAC) was reported as an important cause of morbidity and mortality in advanced HIV infection. It was reported to be the third most common opportunistic infection seen in AIDS patients with an incidence of up to 50% and the third most frequent cause of death in AIDS patients in the USA [11, 79, 80]. Prior to the availability of the protease inhibitors, a diagnosis of d-MAC was associated with shortened survival in HIV-infected individuals [81, 82].

3.3.3 Pathogenesis and clinical features

There is an inverse relationship between the risk of MAC and the CD4 cell count [79, 82]. Diagnosis of MAC is rare except in patients with a CD4 cell count $< 100 \times 10^6$/L [83]. MAC infection may be localised or disseminated, symptomatic or asymptomatic [83]. Presentations of localised disease may include pneumonitis, pericarditis, osteomyelitis and skin abscesses. In the absence of treatment, most individuals with localised disease subsequently develop disseminated disease. Symptomatic MAC infection in AIDS patients most commonly occurs as disseminated multi-organ disease (d-MAC). The most common symptoms of d-MAC are fever, night sweats, diarrhoea, abdominal pain, weight loss, nausea and vomiting. Hepatomegaly, splenomegaly and intra-abdominal lymphadenopathy may occur. The most frequently identified laboratory abnormalities include bone marrow suppression (in particular anaemia) which may be severe, and an elevated alkaline phosphatase.

Diagnosis of d-MAC requires recovery of the organism from a normally sterile site in the body such as blood, bone marrow, or lymph node. Occasionally treatment is instigated empirically on the basis of clinical history. Response to treatment in a symptomatic individual confirms the diagnosis. MAC treatment is discontinued if an alternative cause of symptoms is diagnosed, for example cryptosporidiosis. Occasionally MAC may be identified in an asymptomatic individual but treatment is initiated after a positive culture in the appropriate clinical setting only.

Recently a new clinical syndrome of MAC infection associated with the initiation of HAART in HIV-infected individuals has been reported [84]. A number of researchers have reported the development of focal lymphadenitis commonly associated with draining sinus formation, fever and leucocytosis in patients who have recently commenced HAART. It has been suggested that this clinical presentation is an enhanced immune response to previously subclinical MAC infection. Immune restoration associated with HAART may result in increased numbers of memory CD4 cells specific for mycobacterial antigens. The substantial numbers of new, functionally competent immune cells, which become available as a result of effective antiretroviral therapy, may mount an intense inflammatory response to previously asymptomatic localised MAC infection.

3.3.4 Treatment

Several advances have been made in recent years in the treatment of MAC. Appropriate treatment has been shown to decrease the burden of infection and improve survival. Similar to many other infectious diseases, although monotherapy may temporarily decrease the quantity of mycobacteria in the blood and alleviate symptoms, multidrug regimens are used to maximise efficacy and minimise the development of resistance. The cell wall of mycobacteria inhibits penetration of most antibiotics. Also, MAC is an intracellular

organism with a predilection for the cytoplasm of the macrophage. Taking account of these properties of the mycobaterium, drug selection must reflect an ability to concentrate intracellularly in the macrophage and to penetrate the cell wall of the organism. The rifamycins (rifampicin and rifabutin), the macrolides (clarithromycin and azithromycin), the quinolones (ciprofloxacin, ofloxacin, levafloxacin) and ethambutol effectively penetrate the macrophage and the mycobacterial cell wall [85]. Doses and costs per day are summarised in Table 3.1.

Prior to the introduction of HAART as standard of care in our clinic mid-1996, first line treatment of MAC constituted a triple regimen of clarithromycin/ethambutol/rifabutin. This triple regimen had been evaluated in a randomised comparative study with a 4-drug combination of rifampicin/ethambutol/clofazimine/ciprofloxacin [86]. The 3-drug regimen demonstrated statistically significantly greater benefit in terms of clearance of bacteraemia and survival. In cases of intolerance or suspected resistance to standard therapy, other drugs incorporated into the regimen as second line therapy at our centre included azithromycin, ciprofloxacin, clofazimine and amikacin.

Table 3.1: Regimens for the treatment of *Mycobacterium avium* complex infection prior to and subsequent to the introduction of HAART.

	1st line regimen	Cost per day (IR£)	2nd line agents	Cost per day (IR£)
Pre-HAART	Clarithromycin 500mg bd	3.35	Azithromycin 500mg od	4.98
	Ethambutol 15mg/kg od	0.72	Clofazimine 100mg od	0.09
	Rifabutin 300mg od	5.71	Ciprofloxacin 500mg bd	2.63
			Amikacin 15mg/kg od	23.82
	Cost of regimen	9.78		
Post-HAART	Azithromycin 500mg od	4.98	Rifabutin 300mg od	5.71
	Ethambutol 15mg/kg od	0.72	or Rifabutin 150mg od	2.86
			Clarithromycin 500mg bd	3.35
			Ciprofloxacin 500mg bd	2.63
			Amikacin 15mg/kg od	19.69
			(Clofazimine no longer recommended)	
	Cost of regimen	5.70		

Prices as of December 1998 for 70kg patient

With the introduction of HAART in 1996, it was necessary to modify treatment regimens for MAC because of the clinically significant interaction profile of the rifamycins with the protease inhibitors. The protease inhibitors are substrates for and modulators of cytochrome P450. Rifabutin exhibits a significant interaction profile with the protease inhibitors. There were four protease inhibitors available for use in Ireland by the end of 1998: saquinavir, ritonavir, indinavir and nelfinavir. Saquinavir and ritonavir were available in March 1996, indinavir in May 1996 and nelfinavir in May 1997. Co-administration of rifabutin is contraindicated with saquinavir and ritonavir. Rifabutin induces the metabolism of saquinavir and reduces serum levels below the therapeutic range [87]. In contrast, it is the effect of ritonavir on rifabutin metabolism that precludes concomitant prescription of these two agents. Ritonavir inhibits the metabolism of rifabutin

resulting in accumulation and increased serum levels of both the parent drug and its 25-O-desacetyl metabolite. Increased serum levels of rifabutin and its metabolite increase the risk of dose related toxicity including uveitis, bone marrow suppression and myalgia [87]. Rifabutin may be prescribed concomitantly with indinavir and nelfinavir but at half the normal dose [87]. It has been suggested that the doses of indinavir and nelfinavir should be increased to compensate for induction of liver enzymes by rifabutin. The clinical significance of this interaction is unclear and therapeutic drug monitoring of protease levels may be an appropriate strategy. Should the drug levels of the protease inhibitor be less than the minimum inhibitory concentration for the virus, the dose should be increased accordingly. In Ireland, the non-nucleoside reverse transcriptase inhibitors, nevirapine and delavirdine became available in 1997 and efavirenz became available in 1998. These agents are also metabolised by cytochrome P450 iso-enzymes and therefore co-prescribing with rifabutin may result in clinically significant drug interactions. Co-prescribing of rifabutin with either delavirdine or nevirapine may result in decreased levels of the non-nucleoside reverse transcriptase inhibitor. The manufacturers of delavirdine advise against the combination while the manufacturers of nevirapine are unsure as to the significance of the interaction and advise close surveillance of efficacy. Concomitant administration of rifabutin and efavirenz may result in decreased levels of rifabutin and its active metabolite and therefore the dose of rifabutin should be increased to 450mg daily.

From mid 1996, following adoption of HAART as standard of care, first line therapy of MAC at our centre was altered to include a macrolide and ethambutol only, with rifabutin reserved for use in cases of intolerance or failure to respond to dual therapy alone. This change in policy accorded with IDSA (Infectious Diseases Society of America) guidelines for treatment of d-MAC [88]. Coincident with the adoption of dual therapy with a macrolide and ethambutol as first line regimen for MAC, azithromycin replaced clarithromycin as macrolide of choice. In 1996, the appropriate dose of clarithromycin had become unclear following a MAC treatment study, CPCRA 027, in which patients were

randomised to receive one of four 3-drug regimens [89]. Two of the regimens included clarithromycin at a dose of 1g per day and two at the higher dose of 2g per day. At interim analysis, the higher dose clarithromycin arms were prematurely halted because of an unexpected increase in mortality. No other contributing variable could explain the difference in the two arms. Similar results had been suggested by dose ranging studies of clarithromycin (Abbott protocol M91577). Therefore, prescribing practice was altered so that clarithromycin, which previously was prescribed at doses of 1-2g per day, was no longer prescribed at doses exceeding 1g per day. It is unclear whether the elevated concentrations of clarithromycin (C_{max} increased by 31% and AUC increased by 77%) which would result from prescribing ritonavir with clarithromycin at a dose of 500mg twice daily (1g per day), would be associated with greater toxicity [90]. By contrast, azithromycin exhibits a more favourable drug interaction profile i.e. no significant complexation with hepatic cytochrome P450 [91] and was therefore adopted as macrolide of choice for the management of MAC infection. In addition azithromycin, in contrast to clarithromycin, is unlikely to exhibit clinically significant drug interactions with the non-nucleoside reverse transcriptase inhibitors. Because of its long terminal elimination half-life (68 hours after a single dose) azithromycin may be administered in a convenient once daily dosing schedule. Azithromycin at a dose of 500mg once daily (IR£4.98) is more expensive than clarithromycin, even at a lower dose of 500mg twice daily (IR£3.35).

In cases of intolerance or suspected resistance to first line therapy, other drugs incorporated into the regimen as second line therapy included rifabutin, clarithromycin, ciprofloxacin, and amikacin. Clofazimine is no longer prescribed because of an unexplained increased mortality associated with its use in a single study [92]. Ciprofloxacin shows greater activity *in vitro* against MAC than either ofloxacin or levafloxacin and is therefore currently the quinolone of choice. However, *in vivo* studies demonstrating differential clinical efficacy are lacking. The aminoglycoside, amikacin shows good activity and efficacy against MAC. It is only available as a parenteral preparation, is ototoxic and nephrotoxic and is therefore

not suitable for long term therapy. Amikacin does not exhibit good penetration of the mycobacterial cell wall and therefore must always be used in combination with other agents. This agent's main role is to intensify oral treatment regimens but its use requires close monitoring of renal and aural function.

In the pre-HAART era, patients with d-MAC were prescribed treatment regimens for life. The introduction of HAART has resulted in increased CD4 cell counts and therefore a theoretical decrease in the susceptibility of the individual to opportunistic infection [93-95]. When CD4 cell counts rise above the high-risk threshold, there is some evidence to suggest that treatment could be discontinued. This is dependent on whether or not the functional capacity of the rebounded CD4 cells may be considered equivalent to that of CD4 cells prior to HIV-induced depletion. In our centre, a policy of discontinuing MAC treatment in asymptomatic culture-negative patients who have maintained a CD4 cell count $> 100 \times 10^6/L$ and a low level or undetectable viral load for 3 consecutive visits in a six month period, was adopted in mid-1997.

3.4 Methodology

In our centre, outpatient HIV-related prescriptions are dispensed from the satellite pharmacy located in the HIV outpatient clinic. The satellite pharmacy employs a software application, Cliniscript®, to provide labels for dispensed medications and to record items dispensed in a record file that is unique to each patient. This record includes patient identification, the date of dispensing, name and the strength of the medication, quantity dispensed and the cost, as well as any dosage instructions. Drug usage reports from Cliniscript® were employed to quantify drug usage and expenditure for treatment of MAC infection over the time period from the first day of January 1995 to the last day of December 1998 inclusive.

Initially, drug usage reports were generated for each of the drugs used for treatment of MAC i.e. ethambutol, rifabutin, azithromycin, clarithromycin, ciprofloxacin and clofazimine. Prescription of any of these agents for indications other than MAC was excluded following examination of patient medical notes. A longitudinal profile of MAC treatment was constructed for each patient by searching each patient's prescription history. These profiles included the date of initiation and date of discontinuation of therapy, regimens prescribed and duration in days on each regimen. Reasons for discontinuation of MAC therapy including death were abstracted from patient medical records. Although some patients may have commenced therapy as inpatients, it is not possible to assign inpatient expenditure to individual patients. As this analysis relies on drug expenditure reports to identify disease events, the date of first dispensing from the satellite pharmacy was taken as the date of initiation of therapy. The date of discontinuation of therapy was defined to be the date the dispensed medication would have finished should the medication have been taken as directed.

The following parameters were determined:

- the number of patients on MAC treatment each year from 1995 to 1998.
- the number of patients initiated on MAC treatment each year.
- the number of patients who discontinued and the reasons for same.
- the number of patients who died on therapy.
- duration of MAC therapy since initial diagnosis of MAC to determine the proportion of the cohort initiated on therapy that year and each previous year.
- the number of patient treatment days dispensed each year.
- the average number of treatment days per patient each year.
- the number of treatment days of each regimen dispensed each year and the portion or percentage of the total that each regimen represents.

From 12/2/1998, Cliniscript® in the satellite pharmacy was modified to deal exclusively with HIV outpatients. Prior to this change, the application in the satellite was networked to the Cliniscript® in the main hospital pharmacy and all drug files were common. Therefore,

a drug usage report would include any dispensing of that item to any other area within the hospital. All reports prior to February 1998 had to be refined manually to exclude dispensing to wards within the hospital. Inpatient spending was not included in the analysis of expenditure on MAC pharmacotherapy as expenditure could not be assigned to individual patients nor could usage by non-HIV patients be differentiated.

It is possible to calculate yearly expenditure on each individual drug from the drug usage reports. It was considered that ethambutol was included in the majority of regimens to treat MAC infection. Therefore, initially expenditure on ethambutol was used as an indicator drug to examine trends in overall expenditure on MAC treatment. Subsequently, expenditure on each individual drug used in the treatment of MAC infection between 1995 and 1998 was calculated. Total annual expenditure on MAC therapy was calculated by summing total expenditure on each individual drug used to treat MAC in each year of the study.

In an attempt to assure the quality of the data collected, the number of days of treatment with each drug was calculated using two methods and the results were compared. The number of days of treatment was calculated initially by dividing the annual expenditure on each drug by the cost of a single days treatment. For any drug whose daily dose was variable, the expenditure on each dose regimen was calculated individually and the number of days of treatment calculated subsequently. The other approach involved calculating the number of days of treatment with each drug as the sum of the number of days each patient was treated with a regimen containing that drug. This information was taken from individual longitudinal profiles of drug regimens. The degree of concordance between the two methods was considered acceptable if the difference between the values calculated by each method was less than 10% of the total number of treatment days each year. Average daily expenditure per patient treated was calculated for each year of the study by dividing total annual expenditure on MAC therapy by the number of treatment days.

3.5 Results

3.5.1 Epidemiology and Pharmacoepidemiology

Details of the treated cohort, expenditure on treatment and the regimens employed are summarised in Tables 3.2, 3.3 and 3.4. The number of patients on treatment decreased from 30 in 1995 to 16 in 1998 (Figure 3.1). The number of new cases of MAC infection requiring treatment decreased by 86% over the same time period from 22 patients to 3. The number of patients discontinuing MAC therapy increased over the study period. Two patients discontinued therapy in 1995 in contrast to 6 patients in 1998. Reasons for discontinuing therapy include refusal to take therapy, refutal of an empiric diagnosis or more latterly, discontinuation of maintenance therapy in cases of immune reconstitution.

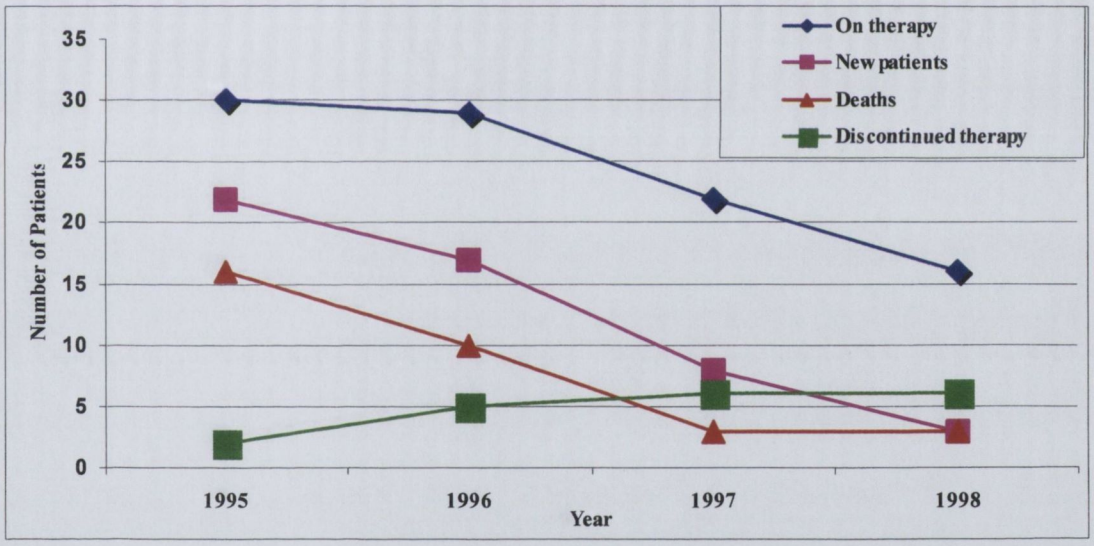


Figure 3.1: Details of patients treated for MAC each year from 1995 to 1998.

Mortality fell from 16 out of 30 patients (53.3%) on MAC treatment in 1995 to 3 out of 16 patients (18.7%) on treatment in 1998 (Figure 3.1). This decline in mortality resulted in an increase in the average length of time from diagnosis with MAC infection to death from 174 days in patients who died in 1995 to 717 days in patients who died in 1998. In 1995, 22 (73%) of patients on therapy were diagnosed that year, 6 (20%) were diagnosed the previous year and only 2 (7%) were diagnosed two years prior to that date. By 1998, only 3

(19%) of the patients were newly diagnosed that year, 2 (12.5%) diagnosed the previous year and the majority (68.5%) were diagnosed two or more years prior to that year (Figure 3.2).

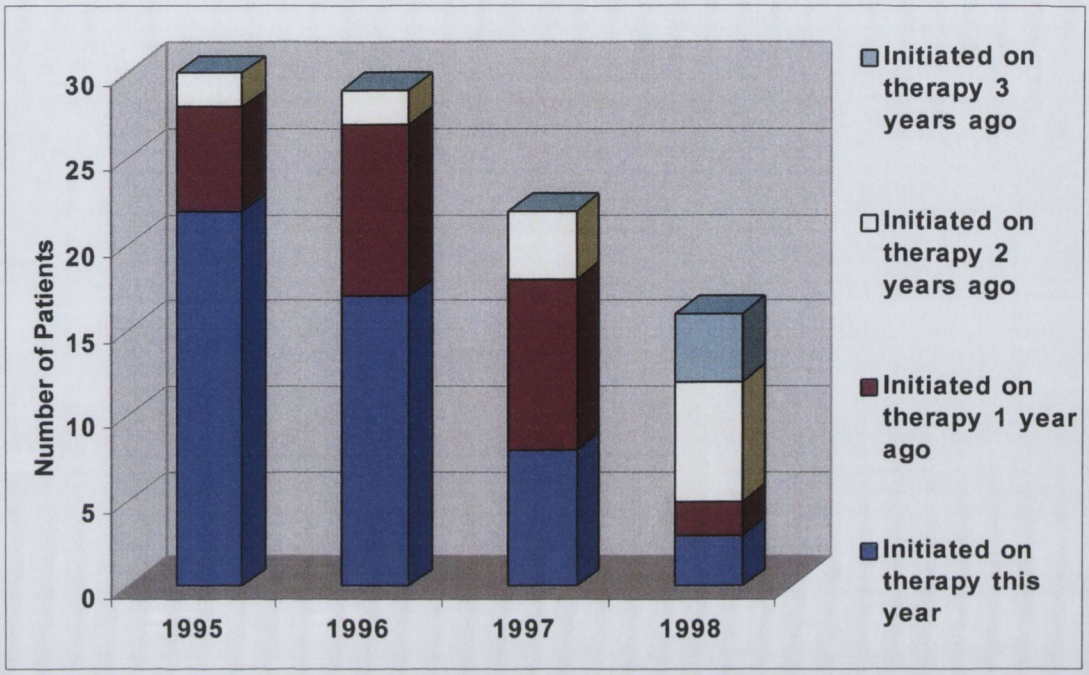


Figure 3.2: Duration on MAC therapy of the treated cohort each year from 1995 to 1998.

On examination of the regimens employed in the treatment of MAC, a number of striking trends in prescribing become apparent. In the first year of the study period, drug regimens including three or more than three agents accounted for 69% of therapy days. The proportion of triple therapy days fell steadily over the 4 years. By 1996, dual therapy accounted for the majority of treatment days. There was a noteworthy decrease in the proportion of rifabutin based regimens from 83% in 1995 to 36% in 1998. During the study period azithromycin replaced clarithromycin as the macrolide of choice. In 1995 azithromycin was included in 9% of macrolide containing regimens and clarithromycin in 91% of regimens. By 1998 clarithromycin was a constituent of only 20% of regimens while 80% of macrolide regimens included azithromycin. Prescribing for the treatment of MAC infection exhibited greater heterogeneity in the earlier years of the study with 9 and

7 different regimens used in 1995 and 1996 respectively in contrast to 5 and 4 different regimens in 1997 and 1998 (Figure 3.3).

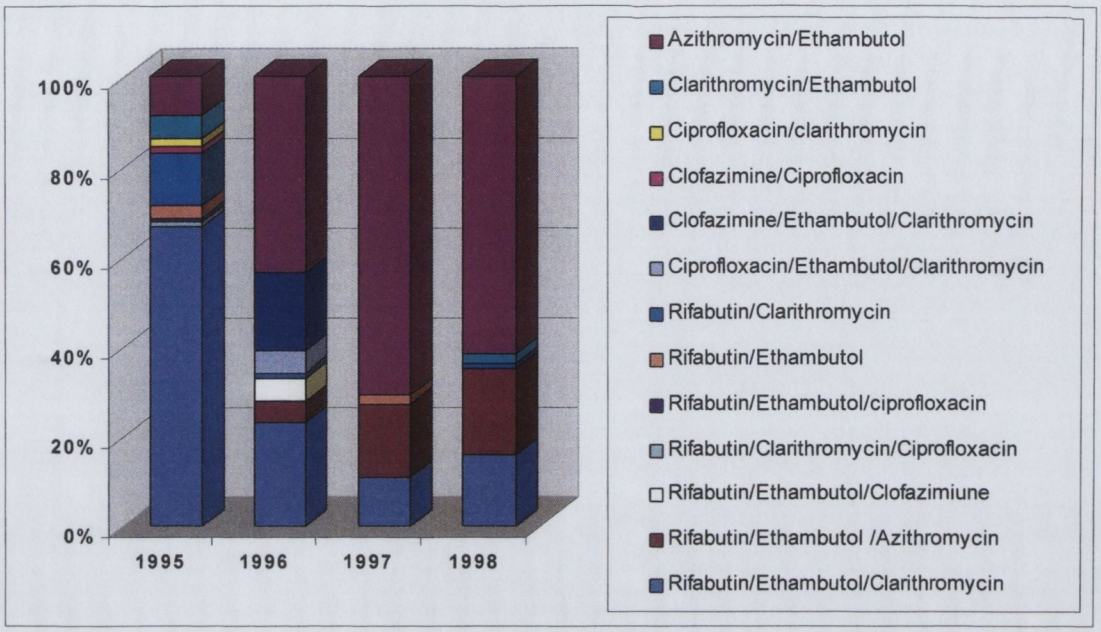


Figure 3.3 Regimens used to treat MAC infection from 1995 to 1998

3.5.2 Pharmacoeconomics

As the numbers of patients on MAC treatment had decreased by almost 50%, a similar trend in the drug acquisition cost of treating MAC infection might have been expected. Ethambutol was included in the majority of treatment regimens (74% in 1995 and 100% in 1998). Although the number of patients on treatment decreased consistently from 1995 to 1998, expenditure on ethambutol increased from IR£1279 in 1995 to IR£2061 in 1996 and IR£2377 in 1997 before falling to IR£1671 in 1998). Therefore, using expenditure on ethambutol as an indicator of total drug expenditure, it suggested that the cost of treating MAC infection did not follow the same pattern as number of patients on therapy.

Total annual expenditure on treatment of MAC infection was calculated and noted to exhibit a similar pattern to expenditure on ethambutol (Figure 3.4). The cost of treatment fell by 20% from IR£24,983 in 1995 to IR£20,025 in 1998 despite a 47% decrease in

number treated over the same time period (Figure 3.5, 3.6). Of note, the cost increased in the intervening 2 years to IR£29,848 in 1996 and IR£30,614 in 1997 before falling to less than 1995 levels in 1998. Contributing factors to annual expenditure include the number of days of treatment dispensed and the cost of the regimens employed. The number of days of treatment increased from 3123 in 1995 to 3536 in 1996, to 4328 in 1997 and then fell to 2768 days in 1998. Agreement between the two methods of determining the number of days of treatment with each drug was within 10% of the number of treatment days each year (4.6%). The mean number of treatment days per patient increased from 104 in 1995 to 122 in 1996, 197 in 1997 and dropped to 173 in 1998. The average daily cost of MAC therapy remained constant decreasing marginally from IR£8.00 in 1995 to IR£7.23 in 1998. Therefore the cost per case treated mirrored the pattern noted for mean number of treatment days per patient.

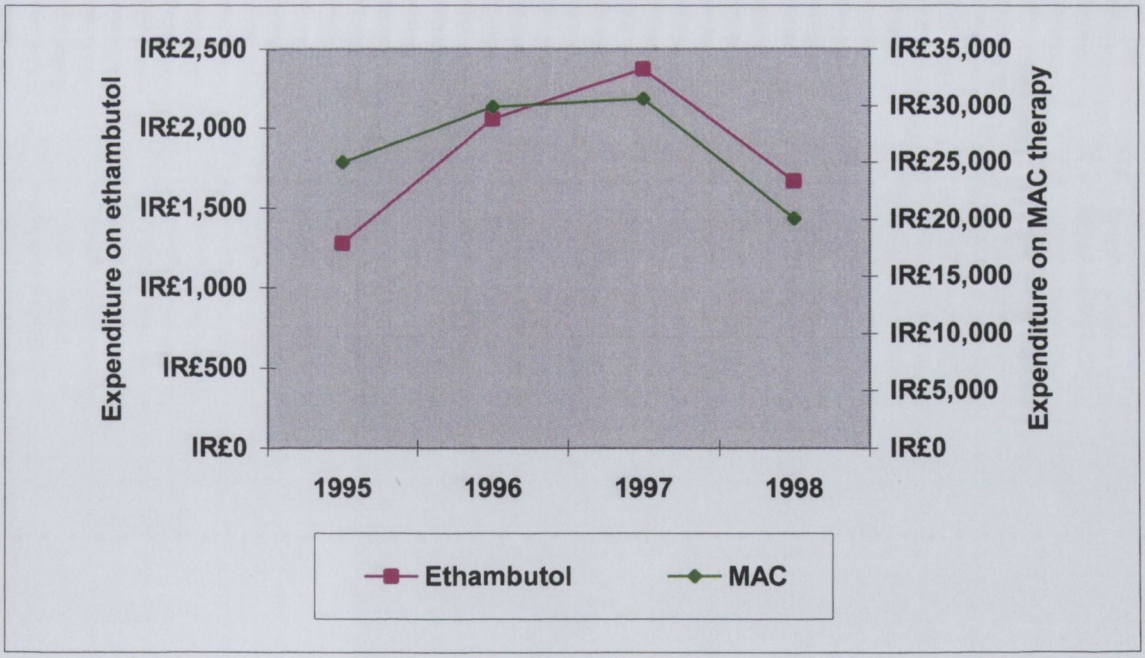


Figure 3.4 Outpatient expenditure on ethambutol and pharmacotherapy of MAC infection from 1995 to 1998.

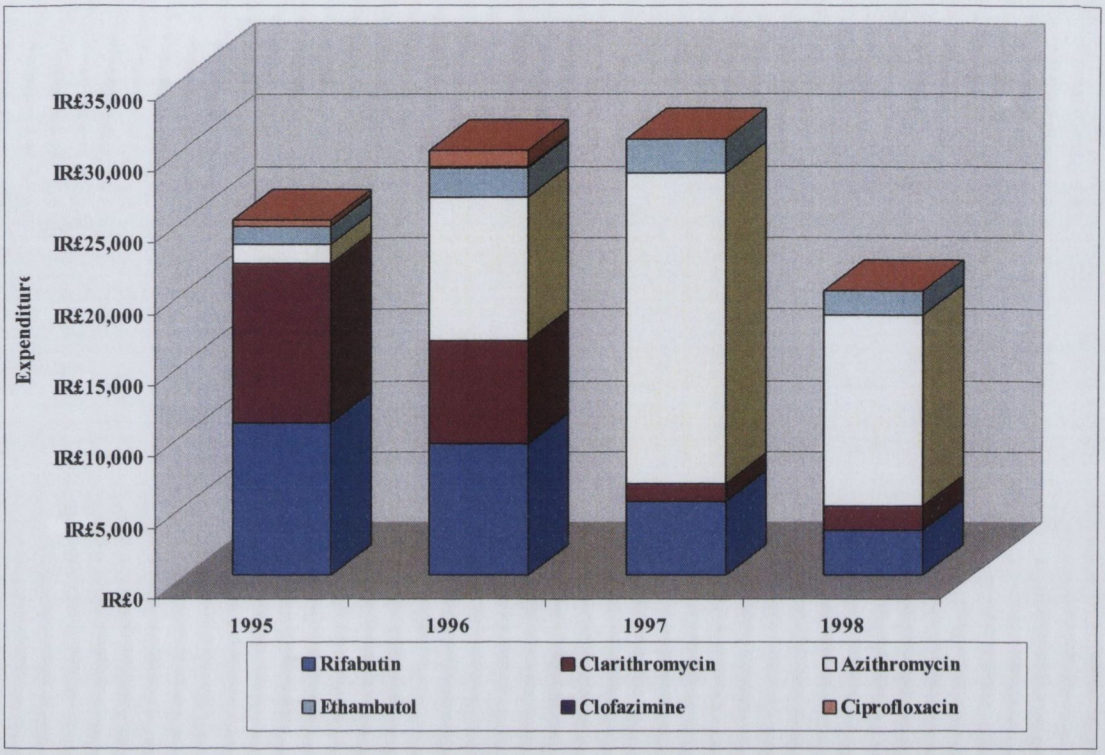


Figure 3.5 **Outpatient expenditure on pharmacotherapy of MAC infection from 1995 to 1998.**

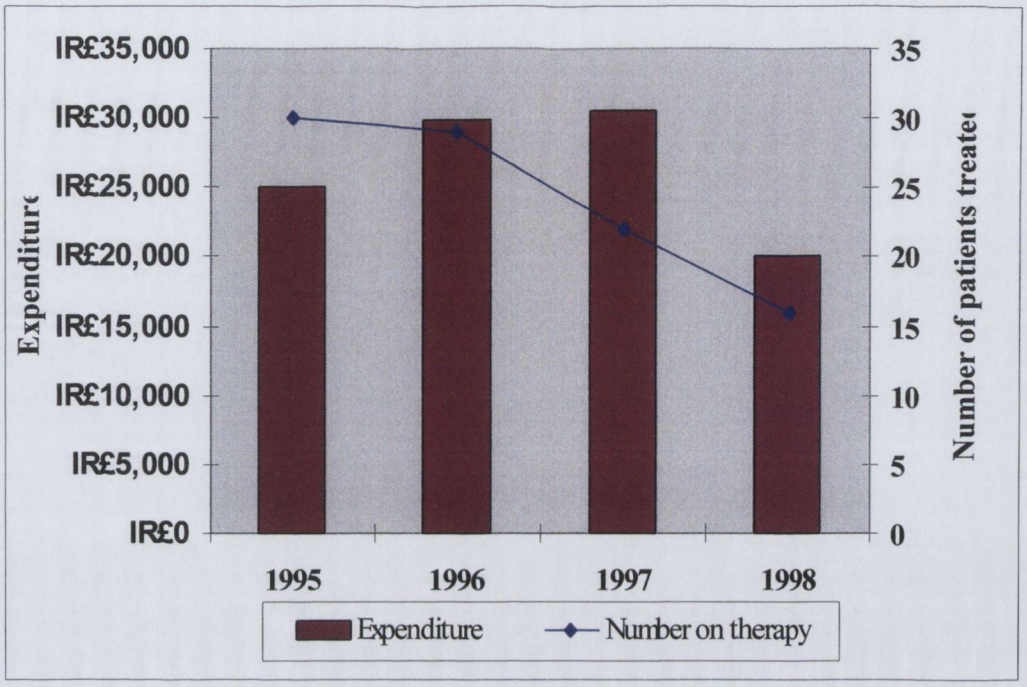


Figure 3.6 **Expenditure on MAC therapy and the number of patients receiving MAC therapy each year from 1995 to 1998.**

Table 3.2: **Details of the cohort treated for *Mycobacterium avium* complex (MAC) each year from 1995 to 1998.**

	1995	1996	1997	1998
Number of patients on MAC therapy each year	30	29	22	16
Number of patients newly initiated on MAC therapy each year	22	17	8	3
Number of patients who died on MAC therapy each year	16	10	3	3
Number of patients who discontinued MAC therapy each year	2	5	6	6
Mean length of time from diagnosis to death in patients who died on MAC therapy each year (days)	173.4	350.7	455.0	716.6

Table 3.3: Details of expenditure on treatment of MAC each year from 1995 to 1998.

	1995	1996	1997	1998
Number of days of therapy for MAC dispensed each year:	3123	3536	4328	2768
Mean number of treatment days per patient treated:	104.1	121.9	196.7	173.0
Expenditure on ethambutol for the treatment of MAC each year (IR£):	1,279	2,061	2,377	1,671
Total expenditure on treatment for MAC each year (IR£):	24,983	29,848	30,614	20,025
Cost per case treated for MAC each year (IR£)	833	1,029	1,397	1,252
Mean daily cost of treatment for MAC (IR£):	8.0	8.4	7.1	7.2

Table 3.4: Details of the treatment regimens employed in the management of *Mycobacterium avium* complex (MAC) each year from 1995 to 1998.

	1995	1996	1997	1998
Proportion of regimens including three or more agents	68.7%	32.8%	27.3%	35.2%
Proportion of regimens including two agents	31.3%	67.2%	72.7%	64.8%
Proportion of regimens including rifabutin	83.0%	34.2%	29.2%	36.1%
The number of different regimens employed	9	7	5	4

3.6 Discussion

3.6.1 Epidemiology and Pharmacoepidemiology

Although mortality in the MAC treated cohort has fallen, the marked decrease in the number of new diagnoses and the increase in the number of patients discontinuing therapy has resulted in an overall decline in the number of patients on treatment from 30 in 1995 to

16 in 1998. The number of new patients fell from 22 in 1995 to 3 newly diagnosed patients in 1998. This dramatic decrease in the number of new patients may be explained by the fact that MAC is a late stage indicator opportunistic infection. The availability of more potent antiretroviral therapy and the switch to prescribing anti-retroviral therapy at an earlier stage of HIV disease i.e. CD4 < 350-500 x 10^6/L rather than < 200 x 10^6/L has halted HIV disease progression and greatly decreased the incidence of those diseases which usually present at lower CD4 cell counts (Table 2.5). Adoption of the newer antiretroviral strategies coincided with an increase in the proportion of our cohort with CD4 cell counts in excess of the high risk threshold for MAC infection (i.e. 100 x 10^6/L) from 63.6% in 1995 to 84.9% in 1998 (Table 2.4). HAART also appears to confer some protective effect against opportunistic infections including MAC in patients who have already progressed to lower CD4 cell counts prior to initiation of antiretroviral therapy. Initiation of HAART results in increased CD4 cell counts in most patients. There has been some debate as to whether universal reconstitution of all CD4 cell clones takes place and therefore whether cellular immunity is as effective as prior to depletion by HIV disease. The decreased incidence of opportunistic infections in such patients post HAART lends evidence to the argument that the reconstituted immune system exhibits some degree of functional capacity.

Following the introduction of HAART, there has been an increase in the number of patients discontinuing MAC treatment. In the pre-protease inhibitor era, treatment for MAC infection, in common with treatment for many opportunistic infections in HIV-infected patients, was lifelong. However, with apparent immune reconstitution in patients responding to HAART, discontinuation of treatment of a number of opportunistic infections has become an option to consider [93-95]. Since mid 1997, a policy of discontinuing MAC treatment in selected patients has been adopted at our centre. MAC treatment was discontinued in 2 patients in 1997 and 5 patients in 1998 in accordance with this policy. No relapses have been documented to date.

The number of deaths amongst patients treated for MAC infection fell from 16 in 1995 to 3 in 1998 (53% to 19%). This decrease in mortality of the MAC treated cohort is a reflection of the overall decline in mortality noted in our cohort. Increased CD4 cell counts and decreased plasma HIV RNA associated with HAART have been shown to be independently associated with greater survival [24]. As described in Chapter 2, the mortality rate in our cohort fell from 16.8 per 100 active patient years in 1995 to 3.5 per 100 active patient years in 1998. Meanwhile, the median CD4 cell count increased from 140 in 1995 to 298 in 1998 and the median viral load declined from 3.94 log copies per ml in 1995 to 3.19 log copies per ml in 1998.

The increased length of time from diagnosis of MAC to death is a reflection of improved morbidity and survival in the era of HAART. The average survival from diagnosis of MAC to death in our centre, of patients who died in 1995 i.e. 174 days, correlates well with reports from other centres in the pre-HAART era [83, 88]. The steady increase in time from MAC diagnosis to death in patients who died each year was temporally coincident with diffusion of HAART through our cohort. By 1998, there was a four-fold increase in survival from MAC diagnosis to death in patients who died that year. As a consequence of increased survival, the duration on therapy profile of the MAC treated cohort also improved over the time period under review. In 1995, the majority of treated patients were initiated on MAC therapy that year. By 1998, only a small proportion were newly diagnosed and most patients were on therapy for two or more years.

Changes in prescribing patterns for treatment of MAC infection were examined. The introduction of HAART in 1996 led to a decrease in the proportion of triple therapy regimens and a decrease in the proportion of rifabutin based regimens. The proportion of rifabutin based regimens dropped steadily from 83% in 1995 to 36% in 1998. This may be explained by the drug interaction profile of the protease inhibitors, which were introduced

in 1996. Rifabutin is contraindicated with saquinavir and ritonavir, the first two protease inhibitors, which became available early in 1996. Rifabutin may be prescribed, albeit at half dose, with indinavir which became available later in 1996, and nelfinavir which was available in 1997. The introduction of the protease inhibitors resulted in a switch from triple drug therapy with clarithromycin/ ethambutol/ rifabutin to dual therapy with azithromycin/ethambutol as first line regimen for treatment of MAC. In 1995, clarithromycin was the most frequently prescribed macrolide antibiotic accounting for 91% of macrolide prescribing. This pattern reversed in 1996 when azithromycin, because of its more favourable drug interaction profile replaced clarithromycin as the macrolide of choice (Figure 3.3). After the introduction of HAART, most patients newly diagnosed with MAC were initiated on azithromycin and ethambutol. The majority of patients who had been prescribed clarithromycin/ethambutol/rifabutin were subsequently changed to azithromycin/ethambutol on commencement of HAART.

Treatment regimens for MAC exhibited less variability in the latter years of the analysis than prior to the introduction of HAART (Figure 3.3). Nine and seven different regimens were prescribed in 1995 and 1996 respectively. Only four regimens were prescribed in 1997 and five regimens in 1998. There are several reasons for this observation. In the post HAART era, patients on MAC therapy are less likely to have relapses of disease which prompt changes in therapy and salvage regimens are required less frequently. Co-administration with protease inhibitors limits the choice of protease inhibitor and the choice of drugs available to treat MAC. Regimens including ciprofloxacin and clofazimine were used for a short period in 1996 after the introduction of protease inhibitors, when an alternative to rifabutin was required. From mid-1996, because of the reports of increased mortality associated with its use, clofazamine was no longer included in treatment regimens as discussed previously. The apparent efficacy, good tolerability and simple once daily dosing of azithromycin/ethambutol soon established it as regimen of choice.

For this chapter, data collection was limited to outpatient prescriptions only. Any treatment of a patient as an inpatient was not captured. Newly diagnosed patients commenced on treatment in hospital were identified initially on the date of discharge prescription. Similarly, treatment of a patient while an inpatient in another hospital or another institution, for example hospice, prison etc. was not captured by this method as medication is provided independently for inpatients by each institution. Nevertheless, on inspection of the data, it is apparent that all patients who were treated for MAC infection were captured in this analysis. In some instances differentiation between *Mycobacteria tuberculosis* (MTB) infection and MAC infection was not available for days to weeks. In the interim, these patients were commenced on rifabutin/isoniazid/clarithromycin/ethambutol to provide anti-bacterial cover for both MTB and non-MTB. In most cases, identification of the mycobacterial species was available and a diagnosis of either MTB or MAC was confirmed prior to discharge. Two patients, who were discharged from hospital on rifabutin/isoniazid/clarithromycin/ethambutol, were subsequently diagnosed as MAC and therefore included in this analysis from date of discharge.

3.6.2 Pharmacoeconomics

In 1995, the majority of patients received three or more drugs, while in contrast, by 1996 the majority of patients were prescribed dual therapy for MAC infection. Also most patients prescribed triple therapy from mid 1996 were prescribed rifabutin at half dose. These changes in prescribing did not result in a dramatic decrease in the cost of MAC therapy per day. The decrease in cost resulting from these changes in rifabutin prescribing was offset to some extent by the switch from clarithromycin to the more expensive azithromycin as macrolide of choice. Clarithromycin at a dose of 1g per day costs IR£3.35 while azithromycin at 500mg per day costs IR£4.98. Also a number of regimens prior to the introduction of HAART included the relatively inexpensive ciprofloxacin and

clofazamine which cost IR£2.63 and IR£0.09 per day respectively. Therefore the resultant change in the average cost of MAC therapy per patient per day was a marginal decrease from IR£8.00 in 1995 to IR£7.23 in 1998.

Ethambutol drug expenditure reports were used as a preliminary analysis of trends in expenditure on MAC treatment. Ethambutol was considered the most useful indicator drug of disease treatment costs because it was included in almost all the regimens used to treat MAC. The disparity between the consistent fall in the number of patients being treated and the initial increase in expenditure on ethambutol in the 2nd and 3rd years of the analysis followed by a decrease in the 4th year prompted an in-depth evaluation of total expenditure on MAC treatment over the 4 year study period. On further analysis it was noted that total drug expenditure on MAC therapy followed a somewhat similar pattern to expenditure on ethambutol (Figure 3.4). While the number of patients on therapy fell consistently over the four year study period, expenditure on drug therapy actually increased over the first three years and then fell in the final year of the study (Figure 3.6).

This apparent paradox may be explained by closer analysis of the data set. Annual drug expenditure is a product of the number of days of therapy dispensed and the acquisition cost of the regimens employed (Figure 3.7). The average cost of therapy per day remained somewhat constant over the study period. Therefore the change in drug expenditure reflects the change in the number of treatment days per year. The number of treatment days is a product of the number of patients on therapy and the mean number of treatment days per patient (Figure 3.7). The number of days of therapy dispensed each year increased in 1996 and 1997 and fell to less than 1995 figures in 1998. The number of patients on therapy fell steadily over the 4-year period. The average number of days on therapy per patient increased between 1995 and 1996, increased further the following year, stabilising at approximately 185 treatment days per patient for 1997 and 1998. The treatment effect of HAART i.e. improved morbidity and longer survival of patients may explain this increase.

The effect of the increased number of treatment days per patient outweighed the effect of decreased number of patients on therapy in the first three years of the study. However, the number of patient treatment days decreased in 1998 due to the discontinuation of 2 patients and the death of 3 others in the first 6 months of 1998 i.e. the effect of the further decrease in patient numbers. Three of the 7 patients who discontinued MAC therapy in 1998 did so in the last three months of the year, which therefore reduced the impact of these discontinuations on the overall number of treatment days.

Annual Expenditure = Number of treatment days/year X mean cost/day

Number of treatment days/year = Number of patients on therapy/year X Mean number of treatment days/patient/year

Figure 3.7 Calculation of annual expenditure and number of treatment days per year for MAC infection.

Since the mean cost per day remained relatively stable, the increased number of treatment days per patient treated was largely responsible for the 50.3% increase in the cost per case treated.

3.7 Conclusion

The impact of HAART on the pharmacoepidemiology and pharmacoeconomics of MAC infection was both qualitative and quantitative. While the number of patients on MAC therapy fell consistently over the study period, initially the number of patient treatment days per year increased, as patients survived longer. By 1998, the continued decline in the

numbers on MAC therapy outweighed the effect of increased survival and the overall number of patient treatment days in 1998 fell for the first time. It is interesting to note that daily cost of MAC therapy decreased by only 9.6% despite a switch from mostly triple MAC therapy to dual therapy, due to the higher acquisition cost of azithromycin, the macrolide of choice in the post-protease inhibitor era. The pattern of drug expenditure paralleled the pattern of patient treatment days. Drug expenditure did not fall to less than pre-HAART levels of 1995 until three years later in 1998. Nevertheless the ongoing policy of discontinuing maintenance therapy in patients who are asymptomatic, virologically suppressed and immunologically stable with CD4 cell counts above the threshold, may be expected to translate into further reductions in expenditure in years to come.

The changes observed in the epidemiology of MAC in our treatment cohort are consistent with the reduction in the incidence and mortality associated with opportunistic infections in the era of HAART reported by us and other centres [12, 46, 60]. There have been dramatic decreases in the number of patients on therapy but the expectation that this would translate into a dramatic decrease in expenditure on MAC therapy has not been realised, at least in the time period under review in this chapter. The cost of treating MAC infection in 1998 was approximately IR5,000 less than in 1995 which is in fact less than the annual cost of treating one patient with HAART. However MAC infection represents only one of the opportunistic infections which present commonly in our cohort. Therefore it was decided to expand this investigation to include an assessment of the impact of HAART on the pharmacoepidemiology and cost of treating a number of other common opportunistic infections.

CHAPTER 4

4 THE IMPACT OF HAART ON THE PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS OF TOXOPLASMOSIS.

4.1 Introduction

Contrary to expectation, the observed decrease in the incidence of MAC disease during the study period was not reflected by a similar decrease in expenditure on pharmacotherapy of this infection (Figure 3.5). In view of the unexpected findings in expenditure on MAC therapy, it was decided to assess changes that occurred in the pharmacoepidemiology and cost of treating a number of other opportunistic infections subsequent to the introduction of HAART. Common HIV-related opportunistic infections are listed in Appendix I. Toxoplasmosis, CMV retinitis and recurrent oral and oesophageal candidiasis were selected for evaluation for a number of reasons. They are amongst the most common opportunistic infections seen in our cohort (Table 2.5). However, unlike the pharmacotherapy of PCP and respiratory tract infection, toxoplasmosis, CMV retinitis and recurrent oral and oesophageal candidiasis are associated with high drug acquisition costs. The impact of HAART on the pharmacoepidemiology and pharmacoeconomics of CMV retinitis and recurrent oral and oesophageal candidiasis will be addressed in subsequent chapters.

4.2 Aim

The aim of this chapter was to examine the impact of HAART on the epidemiology, pharmacoepidemiology and pharmacoeconomics of toxoplasmosis between 1995 and 1998. Any changes in the treatment regimens prescribed were noted, and the pattern of outpatient drug expenditure associated with management of this opportunistic infection was examined.

4.3 Toxoplasmosis

4.3.1 Aetiology

Toxoplasmosis refers to the clinical syndrome caused by *Toxoplasma gondii,* an obligate intracellular parasitic protozoan that infects a variety of warm-blooded animals. Cats are the definitive hosts for *T. gondii*; other mammals including humans are secondary hosts. *T. gondii* is transmitted to humans either by the consumption of contaminated undercooked meat from an infected secondary host or through exposure to cat faeces. In the immunocompetent host, primary infection is usually self-limiting. Many children are exposed to *Toxoplasma gondii* and acute infection is frequently asymptomatic or undiagnosed. Latent infection following acute primary infection is common, usually asymptomatic but tissue cysts may persist for years. While normal host immunity is sufficient to contain the parasite, in the immunocompromised host activation of dormant cysts may occur and result in toxoplasmosis.

4.3.2 Epidemiology

Human infection with *T.gondii* is common with up to 90% of the general population in some countries having toxoplasma antibodies consistent with previous infection [96]. Cerebral toxoplasmosis is the most common opportunistic infection of the central nervous system in HIV-infected individuals. The incidence of toxoplasmosis in HIV-infected patients decreased dramatically with the widespread introduction of co-trimoxazole as PCP prophylaxis, as co-trimoxazole also confers protection against the reactivation of toxoplasmosis [97].

4.3.3 Pathogenesis and clinical features

Cerebral toxoplasmosis is the most common clinical presentation of toxoplasmic infection in HIV-infected patients. Toxoplasmosis usually presents at CD4 cell counts less than 100 x 10^6/L [96]. The most common symptoms are headache, fever, confusion and lethargy. Depending on the site of the brain affected, other clinical features may include weakness, speech disorders, ataxia, apraxia, seizures and sensory loss. Lesions in the basal ganglia may lead to motor deficits. Less frequent manifestations of toxoplasmosis in AIDS patients include ocular disease, which may occur due to reactivation of cysts in the choroid, resulting in chorioretinitis.

As toxoplasmosis in AIDS patients almost always presents as reactivation, patients may have IgG antibodies to *T. gondii* in their serum. The classical findings on computerised tomography brain scan of patients with cerebral toxoplasmosis are multiple ring enhancing space occupying cerebral lesions. Thallium magnetic resonance imaging is more sensitive and may demonstrate multiple lesions not visible on computerised tomography. These changes are not diagnostic of toxoplasmosis as other opportunistic infections and lymphoma may produce similar radiological findings. Definitive diagnosis is only possible by brain biopsy. Due to the invasive nature and attendant risks of this technique and as toxoplasmosis is the most common cause of central nervous system disease in AIDS patients, response to empiric treatment is frequently employed as an initial diagnostic tool. Failure to respond to two weeks of toxoplasmosis therapy suggests the possibility of an alternative pathology and brain biopsy may be required.

4.3.4 Treatment

Patients with toxoplasmosis are treated with induction therapy, which is usually for six weeks or until the signs and symptoms of the infection have resolved or stabilised. In the pre-HAART era, in common with many other opportunistic infections in HIV-infected

patients, discontinuation of therapy was associated with a high rate of relapse [98]. Therefore lifelong maintenance therapy with the same drugs at lower doses was instituted. Apparent immune reconstitution associated with HAART raises the possibility of discontinuing maintenance treatment in patients who are virologically suppressed and immunologically stable with CD4 cell counts above the high-risk threshold for toxoplasmosis [93, 95].

The treatment regimens used are outlined in Tables 4.1 and 4.2. Treatment options for toxoplasmosis include the combination of pyrimethamine with sulphadiazine, clindamycin or a macrolide antibiotic or alternatively atovaquone monotherapy. Sulphadiazine in combination with pyrimethamine has been the treatment of choice for toxoplasmosis since 1988. This combination results in clinical or radiographic improvement in 70 to 90% of patients [99]. Many patients are intolerant of first line therapy. Hypersensitivity to sulphadiazine occurs in 19-34% of HIV-positive patients [100]. The other major use-limiting toxicity of sulphadiazine is crystalluria. Second line therapy in cases of intolerance to sulphadiazine is clindamycin combined with pyrimethamine [101]. In cases of intolerance to second line therapy, for example antibiotic induced colitis with clindamycin, possible alternatives include the combination of pyrimethamine with a macrolide antibiotic i.e. azithromycin or clarithromycin or atovaquone monotherapy [102-105]. None of these third line regimens have been evaluated in comparative studies with standard treatments.

Folinic acid is always co-prescribed with pyrimethamine to prevent pyrimethamine induced haematological toxicity. With the introduction of HAART in 1996, it was necessary to evaluate the potential for clinically significant drug interactions between the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors with other drugs metabolised by cytochrome P450. As there are no known clinically significant interactions between these antiretroviral agents and the drugs used to treat toxoplasmosis, no

adjustment to treatment regimens for toxoplasmosis was required subsequent to adoption of HAART as standard of care[87].

Table 4.1 Induction treatment of toxoplasmosis at St. James's Hospital, Dublin.

	Regimen	Cost of 6 weeks oral induction course (IR£)
1st line therapy	Sulphadiazine 2g four times daily (po/iv) Pyrimethamine 50mg daily* (po) Folinic acid 15mg daily# (po/iv)	235
2nd line therapy	Clindamycin 600mg four times daily (po/iv) Pyrimethamine 50mg daily* (po) Folinic acid 15mg daily# (po/iv)	493
Alternative therapy	Azithromycin 500mg three times daily (po/iv) Pyrimethamine 50mg daily* (po) Folinic acid 15mg daily# (po/iv)	793
Alternative therapy	Atovaquone 750mg qds (po)	1,056

*Pyrimethamine: loading dose of 100mg on Day 1,then 50mg daily.

#Folinic acid: 15mg daily, 30mg daily if evidence of folate deficiency.

Prices as of December 1998.

Table 4.2 Maintenance treatment of toxoplasmosis at St. James's Hospital, Dublin.

	Regimen	Annual cost of maintenance therapy (IR£)
1st line therapy	Sulphadiazine 1g four times daily Pyrimethamine 25mg daily Folinic acid 15mg daily#	1,718
2nd line therapy	Clindamycin 300mg four times daily Pyrimethamine 25mg daily Folinic acid 15mg daily#	2,836
Alternative therapy	Azithromycin 500mg daily Pyrimethamine 25mg daily Folinic acid 15mg daily#	3,232
Alternative therapy	Atovaquone 750mg four times daily	9,177

Folinic acid: 15mg daily, 30mg daily if symptoms of folate deficiency.

Prices as of December 1998.

4.4 Methodology

As described in Chapter 3, drug usage reports from Cliniscript®, the software application employed in the satellite pharmacy in the HIV outpatient clinic, were used to quantify outpatient drug usage and expenditure on the treatment of toxoplasmosis over the study period from the first day of 1995 to the last day of 1998. As before, drug usage reports for each of the drugs prescribed in the management of toxoplasmosis were used to construct longitudinal profiles of toxoplasmosis therapy for individual patients. Data collected included date of initiation of therapy, date of discontinuation, regimens prescribed and duration in days on each regimen. The first date of dispensing from the satellite pharmacy was taken as the date of initiation of therapy. The date of discontinuation of therapy was defined to be the earlier of either the date the dispensed supply of medication would have finished should the medication have been taken as directed, or the date of death. Reasons for discontinuation of therapy including death were abstracted from patients' medical notes.

Therefore the following parameters were calculated:

- the number of patients prescribed maintenance therapy for toxoplasmosis each year
- the number of patients initiated on induction therapy for toxoplasmosis each year
- the number who discontinued therapy and the reasons for same
- the number who died whilst on therapy
- the duration on therapy of those treated each year to enable calculation of the proportion of the treated cohort initiated on therapy that year and in previous years
- the number of days of each treatment regimen dispensed each year and the percentage of the total number of toxoplasmosis treatment days that each regimen represents
- the number of treatment days dispensed each year

Yearly expenditure on each drug was calculated from the drug usage reports. Expenditure on induction and maintenance therapy was evaluated in combination. Therefore the total annual expenditure on outpatient pharmacotherapy of toxoplasmosis was calculated.

In an attempt to assure the quality of the data collected, the number of days of treatment with each drug was calculated using two methods in a similar fashion to that described in Chapter 3 for the MAC data and the results were compared. As before, the degree of concordance between the two methods was considered acceptable if the difference between the values calculated by each method was less than 10% of the total number of treatment days each year.

4.5 Results

4.5.1 Epidemiology & Pharmacoepidemiology

Details of the cohort treated for toxoplasmosis between 1995 and 1998 are summarised in Table 4.3. There was no substantial change in the number of patients on maintenance toxoplasmosis therapy each year. New diagnoses dropped after introduction of HAART in mid 1996. In 1995 there were 9 patients newly diagnosed with toxoplasmosis. This number declined to 6 in 1996 and fell further to 4 and 3 in 1997 and 1998 respectively. Four patients discontinued therapy over the study period; one due to non-compliance, one following refutal of an empiric diagnosis, one transferred care to another centre and one patient's maintenance therapy was discontinued in accordance with a new clinic policy adopted in 1998.

No substantial change in the number of deaths was noted following the introduction of HAART, while there was a considerable increase in the mean length of time from diagnosis with toxoplasmosis to death amongst patients on maintenance toxoplasmosis therapy who died each year. The average duration for patients who died in 1995 was 58.5 days. There was a steady increase in this value each year to 683.3 days in 1998. In 1995, pre-HAART, all patients were on therapy for less than two years. By 1998, 60% of the toxoplasmosis cohort were on therapy for 2 or more years and 20% were on therapy for 4 or more years (Figure 4.1). Patients were prescribed regimens composed of sulphadiazine, clindamycin or azithromycin in combination with pyrimethamine and folinic acid. The proportion of treatment days that can be attributed to each of the therapeutic regimens is demonstrated in Figure 4.2.

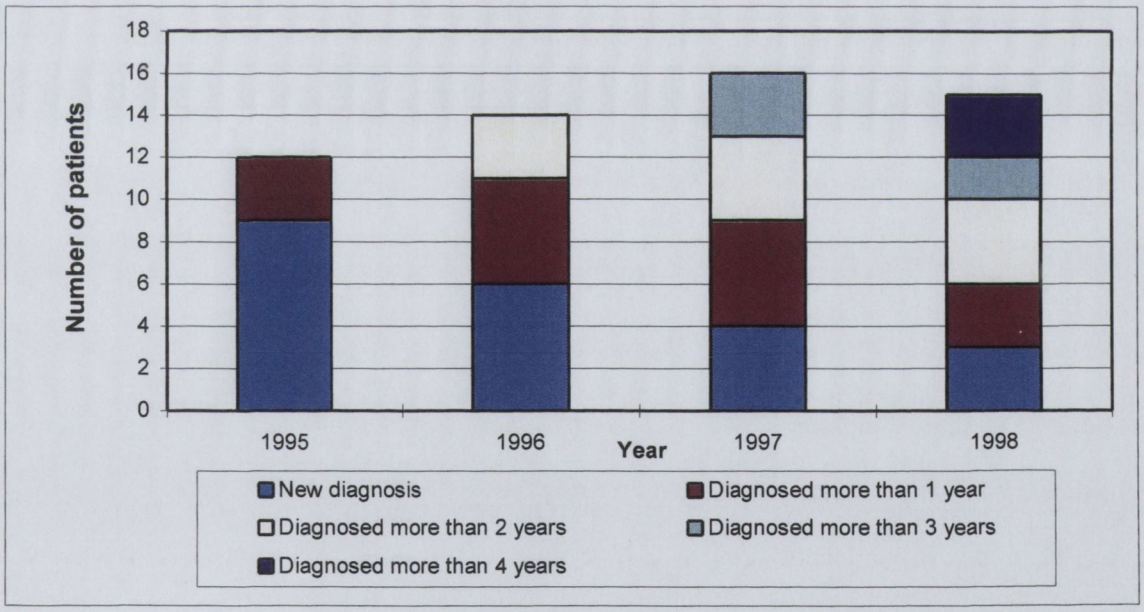


Figure 4.1 Patients treated for toxoplasmosis each year according to the number of years since diagnosis.

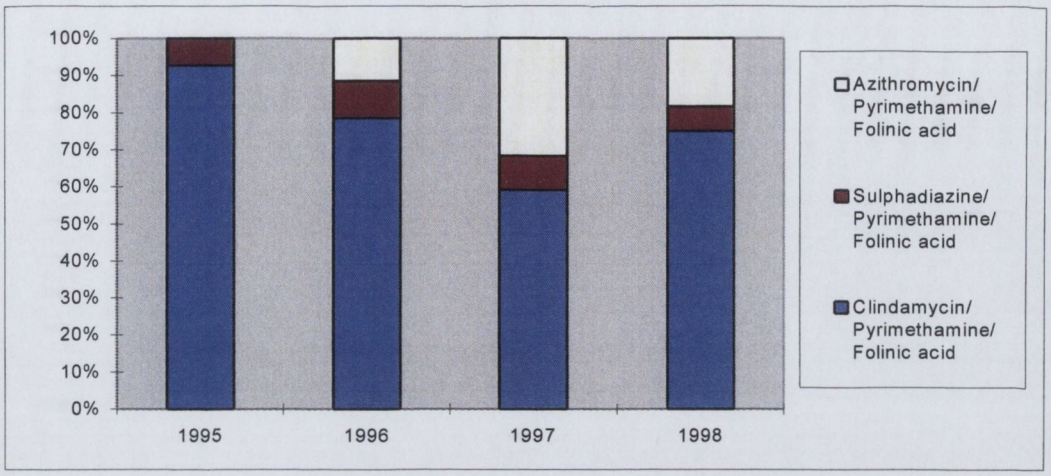


Figure 4.2 Proportion of toxoplasmosis therapy days according to therapeutic regimen each year from 1995 to 1998.

4.5.2 Pharmacoeconomics

Details of expenditure on the treatment of toxoplasmosis from 1995 to 1998 are summarised in Table 4.4. Expenditure on toxoplasmosis increased steadily from IR£11,815 in 1995 to IR£32,168 in 1998 i.e. 172.2% (Figure 4.3). The number of days of toxoplasmosis therapy prescribed each year increased from 1844 days in 1995 to approximately 3100 days in 1996 and 1997 falling to 2914 days in 1998, an overall increase of 58% over the duration of the study. Concordance between the two methods for estimating the number of treatment days was within the specified limit (3.6%). Average daily expenditure on toxoplasmosis therapy increased each year from IR£6.41 in 1995 to IR£11.03 in 1998, representing an overall 72.1% increase over the 4-year period. The cost per case treated increased by 134% from IR£909 in 1995 to IR£2,145 in 1998.

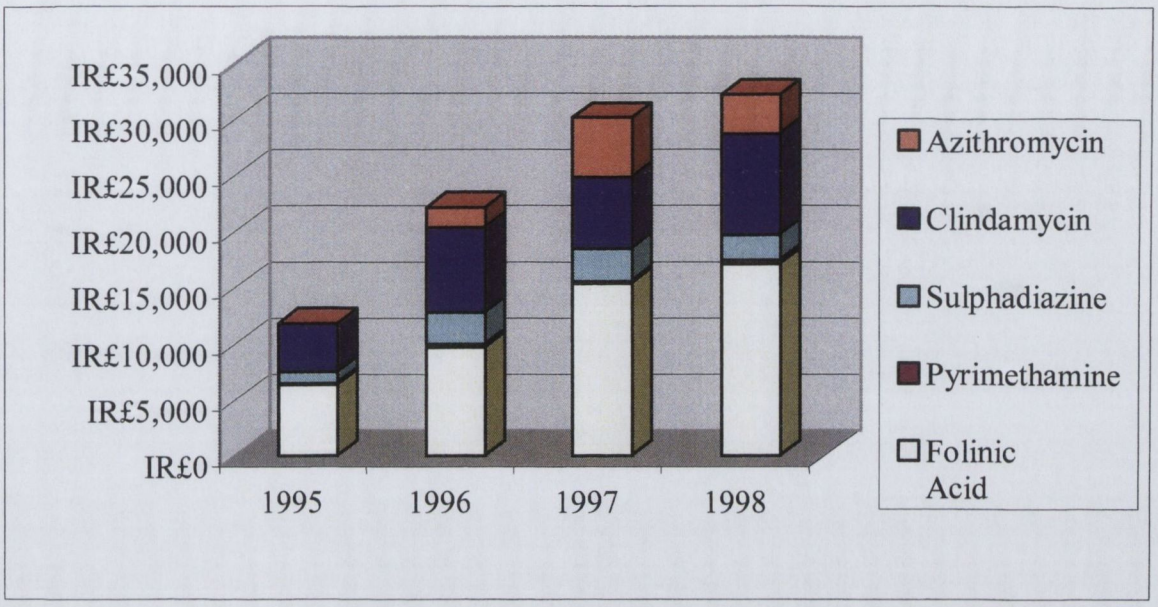


Figure 4.3 Annual expenditure on pharmacotherapy of toxoplasmosis from 1995 to 1998.

Table 4.3 Details of the cohort treated for toxoplasmosis each year from 1995 to 1998.

	1995	1996	1997	1998
Number of patients prescribed maintenance therapy for toxoplasmosis each year	13	14	16	15
Number of patients newly initiated on induction therapy for toxoplasmosis each year	9	6	4	3
Number of patients on maintenance therapy for toxoplasmosis who died each year	3	2	3	3
Mean length of time from diagnosis to death in patients on maintenance therapy for toxoplasmosis who died each year (days)	58.5	360.0	517.3	683.3

Table 4.4 Details of expenditure on management of toxoplasmosis each year from 1995 to 1998.

	1995	1996	1997	1998
Number of days of toxoplasmosis therapy dispensed each year	1,844	3,117	3,100	2,914
Total expenditure on treatment of toxoplasmosis each year	IR£11,815	IR£22,157	IR£30,135	IR£32,168
Cost per case treated for toxoplasmosis each year	IR£909	IR£1,583	IR£1,883	IR£2,145
Mean daily cost of treatment of toxoplasmosis	IR£6.41	IR£7.11	IR£9.72	IR£11.04

4.6 Discussion

4.6.1 Epidemiology & Pharmacoepidemiology

The decrease in the number of new diagnoses in 1998 to one third the number newly diagnosed in 1995, may be explained by the adoption of HAART as standard of care and the decision to initiate antiretroviral therapy earlier in the course of HIV disease in 1996. As a consequence of these changes in antiretroviral policy, the proportion of our cohort with a CD4 cell count below the high risk threshold for toxoplasmosis i.e. CD4 < 100 x 10^6/L decreased from 36.4% in 1995 to 15.1% in 1998 (Table 2.4). An examination of patients' medical notes revealed that the majority of patients in our centre presenting with toxoplasmosis in 1997 and 1998, subsequent to the adoption of HAART as standard of care, were either non-compliant with HAART and PCP/toxoplasmosis prophylaxis or were newly diagnosed with HIV infection, and therefore had not benefited from these potent antiretroviral strategies or prophylaxis regimens. Despite the sharp decrease in the incidence of newly diagnosed toxoplasmosis, the number of patients receiving therapy did not change substantially over the study period because increased survival in the treated cohort led to accrual of patients on therapy.

One patient's maintenance therapy was discontinued in 1998 in accordance with the updated clinic policy on secondary prophylaxis of opportunistic infection. In the pre-HAART era, life long maintenance therapy was considered standard of care. As a consequence of increased CD4 cell counts observed in patients prescribed HAART, it has been suggested that viral suppression and maintenance of the CD4 cell count > 200 x 10^6/L i.e. substantially above the high-risk threshold of 100 x 10^6/L, for at least 6 months may be considered criteria for discontinuation of maintenance therapy for toxoplasmosis [93, 95]. This policy was adopted in our centre in 1998.

Although the number of deaths each year changed little over the study period, a striking increase in survival amongst patients treated for toxoplasmosis was noted. This was reflected by an approximate eleven fold increase in the average number of days from time of diagnosis with toxoplasmosis to death in patients on maintenance toxoplasmosis therapy who died each year i.e. from 58.5 in 1995 to 653 days in 1998. Increased survival amongst patients treated for toxoplasmosis resulted in an improvement in the duration on toxoplasmosis treatment profile of the cohort each year over the study period (Figure 4.1). In the final year of the study, more than half the patients had received toxoplasmosis maintenance therapy for longer than 2 years and 20% for longer than 4 years. These prolonged periods on toxoplasmosis treatment contrast with survival following a diagnosis of toxoplasmosis in the pre-HAART era ranging from 6 to 11 months [106]. Increased duration on therapy coincided with improved survival amongst the HIV-infected cohort as a whole in the era of effective viral suppression associated with HAART. As demonstrated in Chapter 2, the overall mortality rate amongst our cohort declined from 16.8 per 100 active patient years in 1995 to 3.5 per 100 active patient years in 1998. From mid-1996 on, all patients with toxoplasmosis were prescribed HAART.

Intolerance to sulphadiazine amongst HIV-infected individuals has been reported to range between 19 and 34% [100]. Although, sulphadiazine based regimens were considered first

line therapy, the proportion of the total number of treatment days each year attributed to sulphadiazine ranged from 7 to 10% which appears to suggest a higher rate of intolerance in our cohort than previously reported. The reasons for this finding are unknown but patient numbers may be too small to allow definitive estimation of toxicity rates.

4.6.2 Pharmacoeconomics

Expenditure on treatment of toxoplasmosis increased three-fold over the four year time period as a consequence of the increase in the number of treatment days each year and an increase in the average daily cost of therapy over the study period. There was a sharp increase in the number of treatment days between 1995 and 1996, which may be attributed to increased survival subsequent to the intensification of antiretroviral therapy. The number of treatment days did not change substantially in subsequent years but expenditure on treatment of toxoplasmosis continued to increase because average daily cost of toxoplasmosis therapy increased each year over the four years of the study period. Close analysis of the regimens used and the dose of folinic acid employed can explain this trend. The observed increase in the cost per case treated was attributable to the sharp increase in the number of treatment days from 1995 to 1996 and the increase in the cost per day over the four year study period.

Sulphadiazine based regimens are the least expensive. Clarithromycin regimens are more expensive than sulphadiazine and azithromycin is more expensive still (Table 4.1, 4.2). Average daily cost of treating toxoplasmosis increased in the following two years because the proportion of azithromycin days increased in 1996 and 1997. Another contributing factor to increased average daily costs in 1997 was the administration of folinic acid at 30mg per day i.e. double the normal daily dose in 2 patients who had manifested folate deficiency anaemia associated with pyrimethamine despite receiving the normal daily dose of folinic acid of 15mg. This increased requirement for folinic acid manifested in two

patients who had received toxoplasmosis therapy for an unprecedented duration of greater than three years. The average daily cost continued to increase from 1997 to 1998. This occurred despite a decrease in the proportion of azithromycin based treatment days. Double dose folinic acid initiated in two patients in 1997 was continued throughout 1998 and resulted in an overall increase in the average daily cost of treatment for toxoplasmosis. Folinic acid is associated with a high drug acquisition cost and therefore accounted for more than 50% of total drug expenditure on pharmacotherapy of toxoplasmosis during 1997 and 1998. This finding underscores the importance of measuring expenditure on adjunctive therapy in addition to expenditure on the anti-infective constituents of the regimen.

Data collection was limited to outpatient prescriptions only. Any treatment of a patient as an inpatient was not captured. Similarly treatment of a patient while an inpatient at another hospital or institution, for example hospice was not captured by this method, as medication is provided independently for inpatients by each institution. Although the patient numbers are too small to allow any definitive conclusions to be drawn, some trends in the epidemiology and pharmacoepidemiology of toxoplasmosis in this cohort are evident.

4.7 Conclusion

The adoption of HAART in 1996 resulted in a substantial decrease in the number of new diagnoses of toxoplasmosis. However increased survival of HIV-infected patients in the era of HAART has resulted in accrual of patients on maintenance therapy for toxoplasmosis and therefore no decrease in the numbers treated each year. In addition, despite the observed decrease in incidence of toxoplasmosis in the HAART era, increased survival has resulted in an increased number of treatment days per annum with a consequent substantial increase in drug expenditure. An increased dose of folinic acid as adjunctive therapy for a number of patients contributed to an overall three-fold increase in

drug acquisition cost for treatment of toxoplasmosis during the study period. Therefore the hypothesis that decreased incidence of opportunistic infection subsequent to intensification of antiretroviral strategies might translate into cost savings in therapy costs has been completely refuted in the case of toxoplasmosis. In the following chapter, the impact of HAART on the pharmacoepidemiology and pharmacoeconomics of mucocutaneous candidiasis, which is the most common fungal opportunistic infection occurring in our cohort, will be examined.

CHAPTER 5

5 THE IMPACT OF HAART ON THE PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS OF ORAL AND OESOPHAGEAL CANDIDIASIS

5.1 Introduction

The cohort study described in Chapter 2 quantified the impact of HAART on the incidence of commonly occurring AIDS defining illnesses. HIV-related opportunistic diseases, which are not listed in the 1993 CDC classification, were not included in the analysis. Oesophageal candidiasis was diagnosed with an incidence rate of 7.2 per 100 active years prior to the introduction of HAART; thereby constituting the second most common AIDS related disease (Table 2.5). The incidence of oral candidiasis was not determined in the cohort study as it is not classified as an AIDS defining illness [10]. This distinction between oral and oesophageal candidiasis is clinically important but is less useful from a pharmacoeconomic perspective as the same agents are used to treat both presentations and oral candidiasis occurs more commonly than oesophageal disease.

5.2 Aim

The aim of this chapter was to assess the impact of HAART on the pharmacoepidemiology and pharmacoeconomics of oral and oesophageal candidiasis in our cohort.

5.3 Recurrent oral and oesophageal candidiasis

5.3.1 Aetiology

The yeast *Candida* comprises part of the normal flora of the skin, mouth, gastrointestinal tract and vagina. It is present in the oral cavity of 40-60% of the general population but is usually not pathogenic in the immunocompetent host. It can however be pathogenic in immunocompromised patients.

5.3.2 Epidemiology

In the pre-HAART era, oral candidiasis, the most common opportunistic infection in HIV-infected individuals, occurred in as many as 90% of patients at some point during the course of their disease [107]. Oral candidiasis is a clinical indicator of HIV disease progression and mortality and is classified as a Stage B defining illness according to the 1993 CDC criteria for classification of HIV disease [10]. Oesophageal candidiasis, which constitutes the second most common Stage C defining illness, occurs in 15% of AIDS patients, typically when the CD4 count is less than 100 x 10^6/L [108].

5.3.3 Pathogenesis and clinical features.

Oral candidiasis has four distinct clinical expressions: pseudomembraneous, erythematous, hyperplastic and angular chelitis. Diagnosis is based on clinical examination and history. Patients with oral candidiasis may present with symptoms including taste perversion, stomatitis and gingivitis. In most cases, despite the discomfort, patients with oral candidiasis can maintain their oral nutritional intake and avoid weight loss. Oesophageal candidiasis may be diagnosed presumptively on the basis of dysphagia, odynophagia or retrosternal chest pain. Antifungal therapy is usually prescribed without endoscopy. Unlike oral candidiasis, oesophageal candidiasis when severe, can have a substantial impact on oral intake of food resulting in weight loss, patient morbidity and quality of life. Oral and oesophageal candidiasis are frequently recurrent despite treatment.

5.3.4 Treatment

First line treatment of oral candidiasis is usually topical therapy in patients whose CD4 count is close to normal (500 x 10^6/L) [109]. Alternative local therapies include nystatin oral suspension or pastilles and miconazole oral gel. Systemic therapy is indicated in cases of advanced HIV infection, if topical therapy fails or if oesophageal candidiasis is suspected. Agents used include the azoles, amphotericin and flucytosine. The relative

safety of oral azoles has led to their widespread use as first line agents. Fluconazole is the azole of choice while itraconazole is useful if resistance to fluconazole is apparent [110, 111].

Fluconazole is initiated at 50mg daily for oral candidiasis and 100mg daily for oesophageal candidiasis for a period of 5-7 days. If symptoms do not resolve fluconazole is dose increased in a stepwise fashion to a maximum of 400mg daily until response occurs. If symptoms do not respond to high dose fluconazole, itraconazole is prescribed as second line therapy at a dose of 200mg daily increasing to a maximum of 400mg daily for 7 days. If azoles are clinically ineffective because of presumed azole resistance, intravenous amphotericin is prescribed. Amphotericin is reserved as third line therapy because of its toxicity profile, in particular its potential to cause nephrotoxicity and also because intravenous administration requires inpatient or at least day ward admission. Flucytosine exerts a synergistic antifungal activity when co-administered with amphotericin and may be added if symptoms are very severe or slow to respond to amphotericin alone.

With the introduction of HAART as standard of care, the potential for clinically significant interactions between HAART constituents (including the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors) and the antifungal agents used in the management of oral and oesophageal candidiasis was evaluated. Neither the topical anti-fungal agents nor any of the amphotericin formulations have been shown to interact with HAART. The azoles are metabolised by cytochrome P450 and therefore are susceptible to interactions with the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors. Fluconazole may increase the serum concentrations of all of the protease inhibitors but this interaction is not thought to clinically significant [87]. Itraconazole is also an inhibitor of cytochrome P450 and concomitant administration may result in increased protease inhibitor serum concentrations [87]. This interaction may be clinically significant for ritonavir and indinavir and patients should be monitored for signs of

protease inhibitor toxicity, for example increased liver function tests, perioral paraesthesia with ritonavir, nephrolithiasis with indinavir etc. The serum concentration of itraconazole may be increased by ritonavir and lower doses may be sufficient.

The treatment protocol for the management of oral and oesophageal candidiasis in use at our centre is summarised in Appendix III. Azole regimens and costs are summarised in Table 5.1

Table 5.1 Cost of treatment of oral and oesophageal candidiasis.

Regimen	Drug	Dose	Cost for 7 days (IR£)
First line	Low dose fluconazole	50 – 100mg daily	18.40 – 36.80
Second line	High dose fluconazole	200 – 400mg daily	73.59 – 147.18
Third line	Itraconazole	200 – 400mg daily	22.51 – 45.02

5.4 Methodology

As in the cases of MAC and toxoplasmosis, drug usage reports from Cliniscript® were used to quantify outpatient drug usage and expenditure in the treatment of candidiasis during the study period from the first day of 1995 to the last day of 1998. Because of the overlap in treatment regimens, therapy for oral and oesophageal candidiasis was analysed in combination. Use of azoles for management of other fungal infections including cryptococcosis, tinea etc. was excluded following examination of patient medical records. Annual expenditure on each of the oral regimens used in the management of candidiasis was determined from the drug usage reports. The total number of treatment courses with each regimen and the cumulative total expenditure on the management of candidiasis in this population were calculated.

Regimens analysed were classified by convention as follows:

First line therapy	Low dose fluconazole	50mg or 100mg daily for 5-7 days
Second line therapy	High dose fluconazole	200mg or 400mg daily for 5-7 days
Third line therapy	Itraconazole	100mg-400mg daily for 5-7 days

5.5 Results

5.5.1 Pharmacoepidemiology

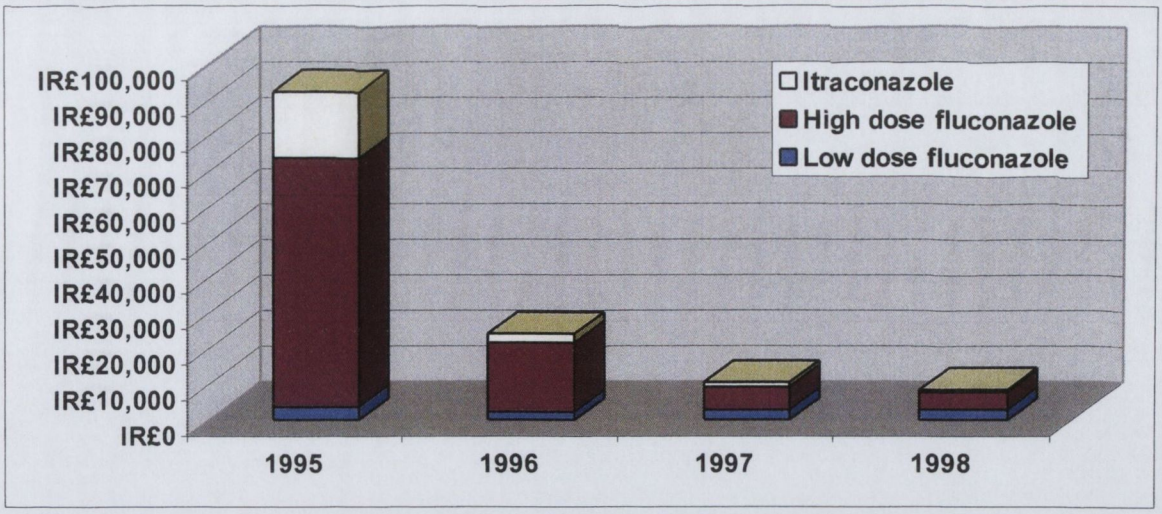
The results are summarised in Table 5.2. The number of outpatient treatment courses prescribed for the management of oral and oesophageal candidiasis decreased substantially from 1128 in 1995 to 378 in 1996 and continued to decline albeit at a lesser rate for the final two years of the study, representing an overall decline of 81.2%. On closer analysis of the regimens used, a shift in the proportion of treatment courses accounted for by first, second and third line therapies was observed (Table 5.2). In 1995, the minority of treatment courses consisted of first line therapy with low dose fluconazole. The majority of patients were treated with either high dose fluconazole or itraconazole as second and third line therapies respectively. The proportion of treatment courses attributable to first line therapy increased each year of the study and accounted for the majority of regimens prescribed from 1997 on. The proportion prescribed third line therapy with itraconazole fell each year of the study from 38.1% in 1995 to 9.9% in 1998. The proportion receiving high dose fluconazole as second line therapy increased initially from 48.8% in 1995 to 58.5% in 1996 but then declined to approximately 30% for the remainder of the study.

Treatment of candidiasis with any intravenous formulation of amphotericin was excluded from the analysis since administration requires hospitalisation or at least day ward admission. There were no outpatient prescriptions of flucytosine during the period under review. As with analysis of the treatment of MAC and toxoplasmosis, data extraction from

Cliniscript® is limited to treatment courses prescribed to outpatients attending the HIV outpatient clinic or on discharge from hospital. Pharmacotherapy of candidiasis by general practitioners or at any other institutions was not captured by this analysis

5.5.2 Pharmacoeconomics

Total expenditure on azoles for the management of oral and oesophageal candidiasis also decreased dramatically between 1995 and 1996 and continued to decline for the last two years of the study representing an overall decrease in cost of 90.7% (Fig 5.1). Expenditure on fluconazole, which accounted for the majority of the budget, increased each year from 79.7% of total expenditure on azoles in 1995 to 91.6% in 1998.



Key: Low dose fluconazole: 50-100mg daily, High dose fluconazole: 200-400mg daily Itraconazole 200-400mg daily

Figure 5.1 Outpatient expenditure on the pharmacotherapy of oral and oesophageal candidiasis according to the regimens employed.

Table 5.2: Details of the treatment for oral and oesophageal candidiasis prescribed in the outpatient clinic each year from 1995 to 1998.

	1995	1996	1997	1998
Total number of treatment courses for oral and oesophageal candidiasis prescribed each year	1128	378	235	212
Number of treatment courses with low dose fluconazole	148 (13.1%)	87 (23.0%)	124 (52.8%)	128 (60.4%)
Number of treatment courses with high dose fluconazole	550 (48.8%)	221 (58.5%)	78 (33.2%)	63 (29.7%)
Number of treatment courses with itraconazole	430 (38.1%)	70 (18.5%)	33 (14.0%)	21 (9.9%)
Total expenditure on pharmacotherapy of oral and oesophageal candidiasis (IR£)	92,325	24,146	10,530	8553
Expenditure on fluconazole (IR£)	73,577 (79.7%)	21,614 (89.5%)	9,272 (88.1%)	7,838 (91.6%)
Expenditure on itraconazole (IR£)	18,748 (20.3%)	2,532 (10.5%)	1,258 (11.9%)	715 (8.4%)

5.6 Discussion

5.6.1 Pharmacoepidemiology

A large decrease in the number of treatment courses prescribed for the management of oral and oesophageal candidiasis was observed between 1995 and 1996 and this decline persisted for the rest of the study. Similar decreases in prevalence have been noted by other centres [112, 113]. The number of treatment courses prescribed includes therapy for both first presentations and recurrences of candidiasis. Therefore, the apparent decline in the frequency of candidiasis as a presentation reflects both a decrease in new diagnoses and a decrease in recurrences. The incidence of new diagnoses of oesophageal candidiasis as an AIDS defining illness declined from 7.2 per 100 active patient years in 1995 to 1.2 per 100 active patient years by 1998 (Table 2.5). The decline in frequency of candidiasis as a presentation may be explained by the sustained improvement in the immunological profile of the cohort over the study period which occurred subsequent to intensification of antiretroviral therapy as described in Table 2.4. There was a sustained increase in the proportion of the cohort with CD4 cell count in excess of 100 x 10^6/L from 63.6% in 1995 to 84.9% in 1998 respectively.

In addition to a decline in the incidence of recurrent oral and oesophageal candidiasis, it has also been noted that improved immunological function secondary to intensification of antiretroviral therapy results in resolution of azole resistant candidiasis in many patients [112, 114]. These findings explain the shift observed in the proportion of treatment courses attributable to different regimens. Coinciding with the improvement in immunological function each year, an increasing proportion of patients responded to first line therapy with low dose fluconazole. This resulted in an overall reduction in the proportion treated with second line therapy with high dose fluconazole from 48.8% in 1995 to 29.7% in 1998 and those treated with third line therapy with itraconazole from 38.1% in 1995 to 9.9% in 1998. A sharp decline in the proportion of patients prescribed third line therapy in 1996

corresponded to an increase in the proportion prescribed second line therapy in the same time period. Further improvement in the immune status of the cohort in subsequent years is evident by a further decline in intensity of the regimens required i.e. a decreased proportion of second and third line regimens and an overwhelming increase in the proportion prescribed first line regimens.

5.6.2 Pharmacoeconomics

Whereas the number of treatment courses prescribed decreased by 81.2% between 1995 and 1998, an even greater decrease in outpatient expenditure on azoles of 90.7% was observed. Fluconazole accounts for the great majority of total expenditure on azoles. High dose regimens carry a drug acquisition cost almost four times that of low dose fluconazole. The number of high dose fluconazole courses decreased by 88.5% over the study period, which contrasts with a 13.5% decrease in the number of low dose fluconazole courses prescribed. The differences in the reduction rates for the two regimens coupled with the much higher drug acquisition cost for high dose fluconazole resulted in a proportionally greater decrease in total drug expenditure than the decrease in the number of courses prescribed.

5.7 Conclusion

The number of azole treatment courses prescribed for the management of oral and oesophageal candidiasis decreased substantially over the study period coincident with an intensification of antiretroviral therapy standard of care. This finding reflects considerable improvement in patient morbidity from Candida infection and resulted in a noteworthy decrease in drug acquisition cost. In the following chapter, the impact of HAART on the pharmacoepidemiology and pharmacoeconomics of CMV retinitis, a late stage indicator disease, which occurs at lower CD4 cell counts than candidiasis, will be examined.

CHAPTER 6

6 THE IMPACT OF HAART ON THE PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS OF CYTOMEGALOVIRUS RETINITIS

6.1 Introduction

CMV is a late stage indicator disease of HIV infection. It occurs at a low incidence rate but is associated with substantial drug acquisition costs. Therefore this disease is a suitable candidate for pharmacoeconomic evaluation.

6.2 Aim

The aim of this chapter was to assess the impact of HAART on the pharmacoepidemiology and pharmacoeconomics of treating CMV retinitis in our cohort.

6.3 Cytomegalovirus Retinitis

6.3.1 Aetiology

Cyomegalovirus (CMV) is a large, double-stranded herpes virus, which can be transmitted through viral shedding in both oral and genital secretions. CMV disease in common with many other opportunistic infections in HIV-infected individuals frequently constitutes a reactivation of latent infection.

6.3.2 Epidemiology

Most of the population demonstrates antibodies to CMV indicating prior exposure at some time. Homosexual intercourse correlates strongly with acquiring CMV infection [115]. Up to 95% of gay men are seropositive for CMV. CMV retinitis is by far the most common clinical expression of CMV disease in AIDS patients accounting for 85% of all presentations [116]. Prior to the introduction of protease inhibitors, the incidence of CMV retinitis in AIDS patients was 14.7 per 100 patient years [61]. Following the adoption of HAART as standard of care in the developed world, the incidence of disease has decreased dramatically with preliminary reports of rates as low as 3.6 per 100 patient years amongst patients with CD4 cell count less than 200 x 10^6/L and 0.65 per 100 patient years amongst

patients receiving HAART regardless of CD4 cell count [46, 61]. The risk of developing CMV retinitis increases markedly with a decline in CD4 cell count. In one study, the average CD4 cell count in patients newly diagnosed with CMV retinitis was less than 30 x 10^6/L [117]. A CD4 cell count of less than 50 x 10^6/L is considered to be the high-risk threshold for CMV disease [118].

6.3.3 Pathogenesis and clinical presentation

CMV retinitis results from the haematogenous spread of CMV after reactivation of latent infection. Untreated, the disease causes a progressive retinal necrosis and loss of vision. Initial symptoms depend on the proximity of the affected area of the retina to the optic nerve or the fovea and may include floaters, flashing lights and decreased visual acuity [119]. CMV retinitis is not usually associated with pain or photophobia. Diagnosis is made after opthalmoscopic examination. Typical presentation on opthalmoscopy includes retinal whitening often associated with intraretinal haemorrhages. Progression of disease may result in retinal detachment. Prior to the availability of anti-CMV treatment, severe visual impairment or blindness as a result of disease progression occurred in most patients who survived longer than six months post diagnosis of CMV retinitis [120, 121]. In the pre-protease inhibitor era, despite induction anti-CMV therapy followed by long-term maintenance therapy, most patients eventually suffered a reactivation of CMV retinitis, which required re-induction therapy [122]. Patients may have experienced several reactivations and reinductions during the course of their disease.

6.3.4 Treatment

Several advances in the treatment of CMV retinitis have been made since the onset of the HIV pandemic. There are a now number of drugs available to treat CMV infection including ganciclovir, foscarnet and cidofovir. Ganciclovir was the first agent to become available for this indication in 1984. Subsequently foscarnet became available on an

unlicensed basis in 1994 and cidofovir in December 1996. Initial clinical endpoint studies to demonstrate efficacy of each of the three available agents to treat CMV, compared immediate versus deferred treatment in non sight threatening peripheral CMV retinitis [123-125]. For each agent, immediate therapy resulted in a similar delay to progression compared to deferred treatment. The only large trial to directly compare two drugs in the treatment of CMV retinitis showed no difference in terms of visual outcome between ganciclovir and foscarnet [125].

Ganciclovir is a nucleoside analogue pro-drug that requires intracellular phosphorylation prior to antiviral activity. Ganciclovir is available as both an intravenous and an oral formulation. The intravenous formulation is used for induction and maintenance therapy of CMV retinitis. The oral formulation of ganciclovir is poorly bio-available (2.6 to 7.3%) resulting in a high pill burden of twelve to twenty-four 250mg capsules daily. However, because of avoidance of complications of intravenous therapy such as the risk of catheter-related infection, the oral formulation of ganciclovir has been used as an alternative for first line maintenance therapy. The most substantial toxicity of ganciclovir is bone marrow suppression, which in the ACTG 071 study resulted in neutropenia in 40% and thrombocytopaenia in 25% of treated patients. Ganciclovir induced neutropenia may be ameliorated with granocyte colony stimulating factor. Recurrent neutropenia may be prophylaxed with intermittent granocyte colony stimulating factor in susceptible individuals. In addition, ganciclovir may cause elevated serum creatinine levels in up to 70% of patients treated [87].

Prior to the availability of cidofovir in Ireland in December 1996, intravenous ganciclovir was considered first line induction and maintenance therapy for CMV retinitis at St James's. On diagnosis, ganciclovir was administered at doses of 10mg/kg/day for an induction period of two to three weeks. Once cessation of disease activity after induction therapy was evident on opthalmological examination, patients were switched to

maintenance therapy for life. In the pre-protease inhibitor era, discontinuation of therapy after induction had been shown to result in further retinal necrosis after 2-6 weeks [122] and therefore maintenance therapy was lifelong. Initial maintenance therapy constituted oral ganciclovir at a dose of 1g three times daily. Reactivation of disease on maintenance therapy required re-induction with intravenous ganciclovir and high dose oral maintenance at a dose of 2g three times daily. Reactivation on high dose oral ganciclovir required intravenous ganciclovir induction as before and subsequent maintenance on intravenous ganciclovir at 6mg/kg/day 5 to 7 days per week.

In those patients who continued to relapse on intravenous ganciclovir, resistance to this agent was suspected and patients were prescribed intravenous foscarnet as second line therapy. Foscarnet was prescribed at 180mg/day for 2-3 weeks as induction therapy followed by 120mg/kg/day on 5-7 days per week as maintenance. Foscarnet use is associated with considerable toxicity including renal impairment and electrolyte abnormalities. Daily administration of intravenous ganciclovir or foscarnet requires a permanent indwelling central venous catheter. Such catheters are susceptible to infection and require careful hygiene. To avoid daily hospital attendance for intravenous administration of these two drugs, portable infusion devices which patients are taught to self-administer are prepared aseptically by the hospital pharmacy. Patients are dispensed one weeks supply of CMV treatment. Supply is limited to one week because of the need for close monitoring of full blood count, renal function and electrolytes. Another approach in patients who continue to relapse on monotherapy is combination therapy with daily infusions of foscarnet and ganciclovir. Foscarnet and ganciclovir act synergistically against CMV. In one study the combination was associated with twice as long a time to progression as monotherapy with either drug [126].

The availability of cidofovir at the end of 1996 revolutionised the management of CMV retinitis. Cidofovir has an extended intracellular half life and a prolonged anti-viral activity

facilitating once weekly administration for induction therapy and administration every two weeks for maintenance therapy [127]. Due to its intermittent administration schedule, cidofovir may be administered in the day ward and a permanent indwelling catheter is not necessary. Because of the convenience of administration of this agent resulting in reduced risk of infection associated with permanent indwelling catheters, cidofovir may be considered an attractive option for therapy of CMV. However cidofovir may cause serious irreversible renal toxicity, which can occur despite aggressive hydration and adjunctive therapy with probenecid. In a number of patients cidofovir may not be suitable as first line therapy because of pre-existing renal dysfunction or because of sulpha-intolerance to probenecid.

A novel therapeutic strategy first used in Ireland in 1996 involved the insertion of an intra-ocular ganciclovir implant. The device releases ganciclovir continuously over a 6-9 month period [128]. The implant results in higher intra-vitreal concentrations of ganciclovir and greater clinical efficacy in the treatment of CMV retinitis than have been achieved with intravenous ganciclovir therapy. Although the device provides an alternative in cases of intolerance or poor response to standard systemic therapies, it does not confer any protection against haematogenous spread of CMV resulting in contralateral ocular or extraocular disease. Therefore, patients are maintained on systemic CMV therapy following insertion of the implant. In addition, use of the implant may result in decreased vision associated with surgical complications including retinal detachment.

The treatment of CMV retinitis requires individualisation on the basis of the patient's underlying medical condition taking consideration of such factors as concomitant medications, co-existing morbidities, history of drug intolerance, the patient's living conditions and lifestyle preferences. The drugs, doses and cost of treating CMV retinitis in a 70kg patient with normal renal function are summarised in Table 6.1. Each of these drugs used in the treatment of CMV requires dose reduction dependent on the patient's renal

function. Pharmacy acquisition costs are quoted for administration to both inpatients and outpatients. Where appropriate the cost of administration in the outpatient setting includes the cost of disposable home infusion devices.

Table 6.1: The drugs and doses employed and the pharmacy acquisition cost per day for maintenance therapy of CMV retinitis in a 70kg patient with normal renal function.

Drug	Inpatient cost/day* IR£	Outpatient cost/day* IR£
Ganciclovir intravenous 6mg/kg daily	31.26	62.72
Ganciclovir oral 1g three times daily	39.07	39.07
Ganciclovir oral 2g three times daily	78.13	78.13
Foscarnet 120mg/kg daily	0.00	78.65
Cidofovir 5mg/kg every two week	55.92	55.92
Ganciclovir intra-ocular implant every six months	14.10	14.10

Costs are quoted for inpatient and outpatient therapy. The outpatient therapy cost includes where applicable the cost of disposable devices for home administration.

* Prices as of December 1998 for 70kg patient.

6.4 Methodology

All of the agents used in the treatment of CMV infection are cytotoxic and therefore intravenous preparations of these agents are produced aseptically by the hospital pharmacy cytotoxic reconstitution service for administration to both inpatients and outpatients. Clinichemo® is a software package employed by the cytotoxic reconstitution service to provide labels for all prepared products and to record in a file unique to each patient all items prepared for that patient. Patient data is categorised according to supervising consultant. Data provided by a dispensed report from Clinichemo® includes patient name, patient location i.e. inpatient, day ward or outpatient, drug, dose and cost. Therefore in contrast to the earlier analyses of MAC, toxoplasmosis and candidiasis that focussed

exclusively on outpatient treatment, it was possible to include inpatient treatment in the analysis of CMV disease.

Dispensed reports for ganciclovir, foscarnet and cidofovir were analysed and data collated to produce a longitudinal treatment profile for each HIV-infected patient who received CMV therapy. Therapy with oral ganciclovir was quantified using dispensed reports from Cliniscript® to identify outpatient dispensing as described previously in the evaluation of other opportunistic infections and using patients' drug prescription records to identify administration to inpatients. Information on reasons for discontinuing therapy, which included death, was abstracted from patient medical records. This analysis was limited to the treatment of CMV retinitis only. Therapy for other manifestations of CMV disease was excluded following examination of patient medical records. The longitudinal treatment profiles produced for each patient included dates initiated on induction and maintenance courses, regimens employed and the costs thereof.

The following data was extracted from the longitudinal treatment profiles produced for each patient:

- number of patients on CMV therapy each year
- number of patients newly initiated on CMV therapy each year
- number of patients who died on therapy each year
- number of patients who discontinued CMV therapy each year
- duration and cost of induction and maintenance therapy
- duration and cost of therapy with each of the agents used to treat CMV
- duration and cost of inpatient and outpatient therapy

The study period ran from the first day of January 1995 to the last day of December 1998. If ganciclovir or foscarnet was prepared for self-administration by the patient at home, the cost of the disposable portable infusion devices was included in the cost calculated by Clinichemo®. Costs of intravenous medication and the infusion devices in addition to

ganciclovir implants were inclusive of value added tax (VAT) at a rate of 21%. The oral formulation of ganciclovir, as is the case for all oral medication is exempt from VAT.

6.5 Results

6.5.1 Epidemiology and Pharmacoepidemiology

Details of patients treated for CMV retinitis are summarised in Table 6.2. The number of patients treated for CMV retinitis fell each year of the study from thirteen patients in 1995 to two patients in 1998. The number of patients newly diagnosed with CMV retinitis declined each year from six patients in 1995 to only one patient in every subsequent year of the study period. Five patients died in 1995, six in 1996, two in 1997 and no patient died on CMV therapy in 1998. One patient discontinued therapy during the study period.

The number of CMV treatment days decreased consistently each year of the study from 3288 days in 1995 to 585 days in 1998 representing an overall 5.6 fold decline (Table 6.3). The number of ganciclovir and foscarnet treatment days varied throughout the study period but the proportion of annual treatment days attributed to ganciclovir was always considerably greater than the proportion accounted for by foscarnet. Cidofovir was prescribed for the first time in 1997 and accounted for the largest proportion of treatment days attributed to any agent in that year (57.7%). The proportion of treatment days with cidofovir fell however in 1998 to just 10.6%. The majority of treatment days each year were accounted for by maintenance therapy.

6.5.2 Pharmacoeconomics

Total expenditure on the pharmacotherapy of CMV retinitis decreased consistently over the study period from IR£182,421 in 1995 to IR£27,437 in 1998 representing a 6 fold reduction over the study period (Table 6.4). There was an overall reduction in the proportion of total expenditure attributed to ganciclovir each year over the study period from 93.6% in 1995 to 57.9% in 1998, coincident with a sustained increase in the proportion accounted for by foscarnet each year and the availability of cidofovir from the end of 1996 onwards. Foscarnet is available in Ireland on a named patient basis only and is provided by the manufacturer free of charge. Therefore costs attributed to foscarnet in this assessment represent where applicable the cost of disposable devices for home administration only. Cidofovir accounted for 27.6% of expenditure in 1997, its first year of use. The proportion of total expenditure associated with cidofovir declined to 11.4% in 1998. Maintenance therapy accounted for the majority of treatment costs for CMV retinitis during each year of the study. The proportion of expenditure accounted for by maintenance therapy increased each year from 1995 to 1997 and then declined in 1998. The proportion of total pharmacy acquisition costs accounted for by treatment of outpatients increased from 42.0% in 1995 to 80.7% in 1998.

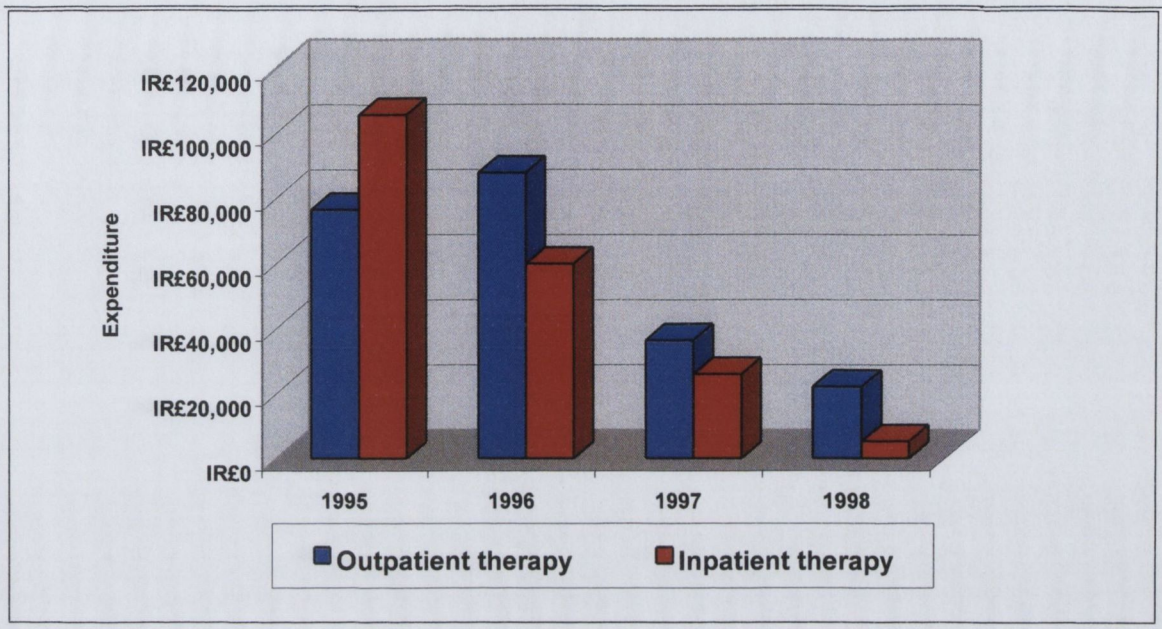


Figure 6.1: Inpatient and outpatient expenditure on treatment of CMV retinitis each year from 1995 to 1998

Table 6.2: Details of the cohort treated for CMV each year from 1995 to 1998

	1995	1996	1997	1998
Number of patients on CMV therapy each year	13	9	4	2
Number of patients newly initiated on CMV therapy each year	6	1	1	1
Number of patients who died on CMV therapy each year	5	6	2	0
Number of patients who discontinued CMV therapy each year	0	0	1	0

Table 6.3: The number of CMV retinitis treatment days each year from 1995 to 1998 according to drugs prescribed and according to induction and maintenance therapy.

	1995	1996	1997	1998
Number of CMV treatment days	3288	2305	1349	585
Number of ganciclovir treatment days	3095 (94.1%)	1686 (73.1%)	353 (26.2%)	343 (58.6%)
Number of foscarnet treatment days	193 (5.9%)	619 (26.9%)	217 (16.1%)	180 (30.8%)
Number of cidofovir treatment days	0 (0%)	0 (0%)	779 (57.7%)	62 (10.6%)
Number of induction treatment days	506 (15.4%)	229 (9.9%)	25 (1.9%)	166 (28.4%)
Number of maintenance treatment days	2782 (84.6%)	2076 (90.1%)	1324 (98.1%)	419 (71.6%)

Table 6.4: Pharmacy acquisition costs of treating CMV retinitis each year from 1995 to 1998. Costs are expressed as expenditure on individual agents, expenditure on induction and maintenance therapy and expenditure on treatment of inpatients and outpatients.

	1995	1996	1997	1998
Total expenditure on treatment of CMV each year	**IR182,421**	**IR147,777**	**IR62,302**	**IR27,437**
Expenditure on ganciclovir therapy	IR£170,781 (93.6%)	IR£114,429 (77.4%)	IR£27,538 (44.2%)	IR£15,890 (57.9%)
Expenditure on foscarnet therapy	IR£11,640 (6.4%)	IR£33,348 (22.6%)	IR£17,539 (28.2%)	IR£8,416 (30.7%)
Expenditure on cidofovir therapy	IR£0.00 (0.0%)	IR£0.00 (0.0%)	IR£17,225 (27.6%)	IR£3,131 (11.4%)
Expenditure on induction therapy	IR£27,082 (14.8%)	IR£11,074 (7.5%)	IR£0.00 (0%)	IR£5,771 (21.0%)
Expenditure on maintenance therapy	IR£155,34 (85.2%)	IR£136,703 (92.5%)	IR£62,302 (100.0%)	IR£21,666 (79.0%)
Expenditure on inpatient therapy	IR£105,833 (58.0%)	IR£59,906 (40.5%)	IR£25,938 (41.6%)	IR£5,306 (19.3%)
Expenditure on outpatient therapy	IR£76,588 (42.0%)	IR£87,871 (59.5%)	IR£36,364 (58.4%)	IR£22,131 (80.7%)
Outpatient cost per case treated	IR£5,891	IR£9,763	IR£9,091	IR£11,065

Note: Where appropriate, costs include the cost of disposable devices for home administration. Foscarnet is available on an unlicensed basis only in Ireland and is provided by the company free of charge. Costs attributed to foscarnet in this table include the cost of disposable devices for home administration only.

6.6 Discussion

6.6.1 Epidemiology and Pharmacoepidemiology

A substantial decrease in the number of patients prescribed therapy for CMV retinitis was noted during the study period. This occurred mainly as a result of the dramatic decline in the number of patients newly diagnosed from six patients in 1995 to just one patient in each of the subsequent years. As with the other opportunistic infections assessed, this decline in numbers treated and in numbers newly diagnosed, coincided with intensification of antiretroviral therapy and the adoption of HAART as standard of care. There was an overall decrease in the number of patients who died on therapy each year during the study period. This finding is consistent with the decrease in mortality rate in our cohort from 16.8 per 100 active patient years in 1995 to 3.5 per 100 active patient years in 1998 as described in Chapter 2.

In contrast to the evaluation of other opportunistic infections, which was limited to outpatient prescriptions only, it was possible to analyse complete treatment courses of CMV therapy administered to both inpatients and outpatients. The number of treatment days for CMV retinitis fell substantially over the study period reflecting the decline in the number of patients on therapy. The proportion of treatment days attributed to ganciclovir always exceeded that attributed to foscarnet. This finding was unsurprising since foscarnet was always considered to be second choice to ganciclovir because of its less favourable tolerability profile. Cidofovir was first used at our centre in 1997. Cidofovir may be considered as an attractive alternative to other intravenous agents because of its convenient intermittent administration schedule, which does not necessitate the insertion of a permanent indwelling intravenous catheter. Since 1997, cidofovir administered every two weeks has constituted an alternative strategy to administration of ganciclovir or foscarnet for maintenance therapy of CMV retinitis five to seven days weekly. In addition, due to the high costs of the self-administration devices for ganciclovir and foscarnet, pharmacy costs

for cidofovir therapy are approximately equal to the cost of outpatient administration of the other two agents if prescribed 5 out of 7 days and considerably cheaper if prescribed 7 days a week. In 1997, three of four patients on maintenance therapy were prescribed cidofovir thereby explaining the substantial proportion of treatment days (57.7%) attributed to this agent. Two of these patients died that year. Cidofovir therapy was discontinued in the third patient because of associated renal toxicity. Cidofovir accounted for only 10.6% of treatment days in 1998. Two patients received therapy for CMV retinitis in that year. One patient had been prescribed cidofovir therapy the previous year but discontinued due to toxicity as mentioned earlier. The other patient was prescribed cidofovir in 1998, which was subsequently also discontinued because of renal toxicity. Despite its favourable administration schedule, cidofovir is associated with a considerable renal toxicity profile as illustrated by this small treatment series. Renal toxicity demonstrated in this setting occurred despite aggressive hydration, prophylactic use of probenecid as adjunctive therapy and dose reduction in renal dysfunction as advised by the manufacturer. The apparently favourable cost benefit ratio associated with cidofovir in particular in the outpatient setting, may be compromised to some extent because of use-limiting toxicity.

6.6.2 Pharmacoeconomics

Ganciclovir, which is considered first line therapy for induction and maintenance therapy of CMV, accounted for a decreasing proportion of treatment costs over the study period. Increased duration on therapy may have resulted in the acquisition of resistance to ganciclovir therapy and therefore the increased requirement for alternative agents such as foscarnet and cidofovir. As mentioned earlier, three of the four patients on maintenance therapy were prescribed cidofovir in 1997 and therefore cidofovir accounted for a considerable proportion of the budget in its first year of use (27.6%). However both patients who received maintenance therapy in 1998 discontinued cidofovir because of renal toxicity thereby resulting in a decline in the proportion of total expenditure on cidofovir in

1998 to just 11.4%. Despite the fact that foscarnet was supplied free of charge, therapy with this agent accounted for 6.4% of total costs in 1995 and for between 20% and 30% of total costs in the years thereafter. This may be explained by the high acquisition cost of the disposable device for foscarnet home infusion at IR78.65 per day.

Maintenance therapy accounted for the majority of treatment costs each year. In 1997 the cost associated with induction therapy was zero. Two patients received induction therapy in that year. Both patients were treated with high dose foscarnet as induction therapy and received the entire treatment course as inpatients. Therefore since the drug acquisition cost of foscarnet is zero and no home infusion devices were employed, the cost of induction therapy in that year was also zero. The cost of hospitalisation to receive therapy was not included in this analysis.

The proportion of total expenditure on CMV therapy associated with treatment of outpatients increased substantially over the period under review from 42.0% of total costs in 1995 to 80.7% in 1998. This finding coincides with the decrease in hospitalisation rate of our cohort from 92.2 per 100 active patient years in 1995 to 51.2 per 100 active patient years in 1998 (Table 2.6). Decreased hospitalisation and consequent increased outpatient therapy reflect the overall improvement in morbidity observed in the cohort coincident with the adoption of more effective antiretroviral strategies.

Outpatient expenditure increased between 1995 and 1996 coincident with a shift towards outpatient treatment (Figure 6.1). Outpatient therapy of this disease is associated with higher drug costs than inpatient therapy. The effect on total drug cost of therapy of an increase in the proportion administered on an outpatient basis was offset by use of the less expensive cidofovir and reduced doses of anti-CMV therapy in patients treated in the latter years of the study. Renal impairment attributed to long term therapy for CMV retinitis resulted in reductions to between one third and a half of the doses normally employed and

consequent reductions in drug acquisition costs. Despite an almost doubling of the proportion of overall treatment costs assigned to outpatient therapy, the annual cost of outpatient therapy of CMV retinitis fell by 71.1% over the study period. The overall 87.8% increase in the cost per case treated over the study period was offset by the sharp decrease in the number of patients treated each year.

6.7 Conclusion

The 5.6 fold decrease in the number of treatment days, the use of the less expensive agent cidofovir and the reduced acquisition cost of other agents due to lower doses in patients with renal impairment resulted in a 6.6 fold decrease in the total annual pharmacy acquisition costs of treating CMV retinitis between 1995 and 1998. Expenditure on outpatient therapy decreased by 71.1% over the same time period from IR£76,588 in 1995 to IR£22,131 in 1998. Intensification of antiretroviral therapy and the expansion in the proportion of the cohort treated with HAART over the study period appears to correlate with an overwhelming decline in incidence, morbidity and cost of treating this end stage indicator opportunistic infection.

6.8 Impact of HAART on pharmacoepidemiology and pharmacoeconomics of MAC, toxoplasmosis, oral and oesophageal candidiasis, and CMV retinitis.

Intensification of antiretroviral therapy over the time period under review, in particular the adoption of HAART as standard of care, coincided with a number of interesting changes in the epidemiology, pharmacoepidemiology and cost of treating opportunistic disease.

6.8.1 Epidemiology and Pharmacoepidemiology

A decline in the incidence of toxoplasmosis, CMV and MAC and a decrease in the number of treatment courses prescribed for oral and oesophageal candidiasis was noted. In the case of patients treated for MAC and candidiasis, a reduction in the proportion of patients requiring second line or salvage regimens occurred, thereby reflecting additional improvement in the degree of morbidity associated with opportunistic disease. Opportunistic infections in HIV-infected patients have been associated with progression of HIV disease and death. The decrease in the mortality rate and the increased duration on maintenance therapy amongst patients treated for opportunistic infections as noted in this chapter reflects the overall increase in survival associated with HAART. Immune reconstitution in patients treated effectively with HAART resulting in novel presentations of a number of opportunistic infections including MAC and CMV retinitis has been reported by other centres [84, 129, 130]. However, no cases of immune reconstitution disease were noted in our cohort during the study period.

Pharmacotherapy of the opportunistic infections under review altered somewhat during the study period. Modification of a number of treatment regimens became necessary subsequent to the adoption of HAART as standard of care because of the significant drug interaction profile of the constituent agents. In the pre-HAART era, life long maintenance

therapy for MAC, toxoplasmosis and CMV retinitis was considered standard of care. Following immune reconstitution associated with effective viral suppression with HAART, it has become possible to discontinue maintenance therapy for these opportunistic infections in patients who sustain immunological and virological success.

6.8.2 Pharmacoeconomics

There was an overall decrease in aggregate outpatient expenditure on the management of the four opportunistic infections assessed over the study period (Figure 6.2). However, close examination of expenditure on each of the individual infections reveals contrasting patterns (Figure 6.3). Expenditure on MAC therapy initially increased for the first three years of the study and then decreased. The cost of treating toxoplasmosis increased continuously each year of the study. The outpatient cost of treating CMV retinitis increased initially and then decreased whereas expenditure on pharmacotherapy of candidiasis decreased steadily over the study period. Expenditure on the management of each opportunistic infection depended on the interplay of a number of factors. Alteration of MAC regimens to take account of significant drug interactions with HAART constituents resulted in a change in the mean daily cost of therapy. Increased survival amongst patients resulted in an increase in the number of treatment days per year for patients treated for toxoplasmosis and initially for MAC. However, adoption of a policy of discontinuing maintenance therapy in patients who respond immunologically and virologically to HAART will result in further reductions in the number of treatment days and therefore in the cost of therapy in the future. The total cost of outpatient treatment of the four opportunistic infections included in this assessment decreased by 59.7% from IR£205,712 in 1995 to IR£82,877 in 1998. This resulted in a 71.9% decrease in the cost of treating the four opportunistic infections per active patient in the cohort from IR£641 per active patient in 1995 to IR£180 per active patient in 1998. The more substantial decrease in the cost per

patient than in the total cost is explained by the increase in the size of the active cohort over the 4 years of the study (Table 2.1).

The decrease in the incidence of opportunistic disease and consequent reduction in morbidity and risk of mortality evident over the study period is substantial. The extent to which the increased cost of antiretroviral therapy is offset by the reduced cost of managing these four opportunistic infections is small. However, this analysis does not take consideration of cost savings associated with the reduction in rate of admission for management of these opportunistic infections and for other indications, which has been observed in this cohort temporally coincident with adoption of more effective antiretroviral strategies. Assigning a monetary value to the observed reduction in inpatient days would further contribute to an estimation of the pharmacoeconomic impact of adopting HAART as standard of care. In the next chapter, the cost of inpatient care for HIV-infected individuals at our centre will be determined.

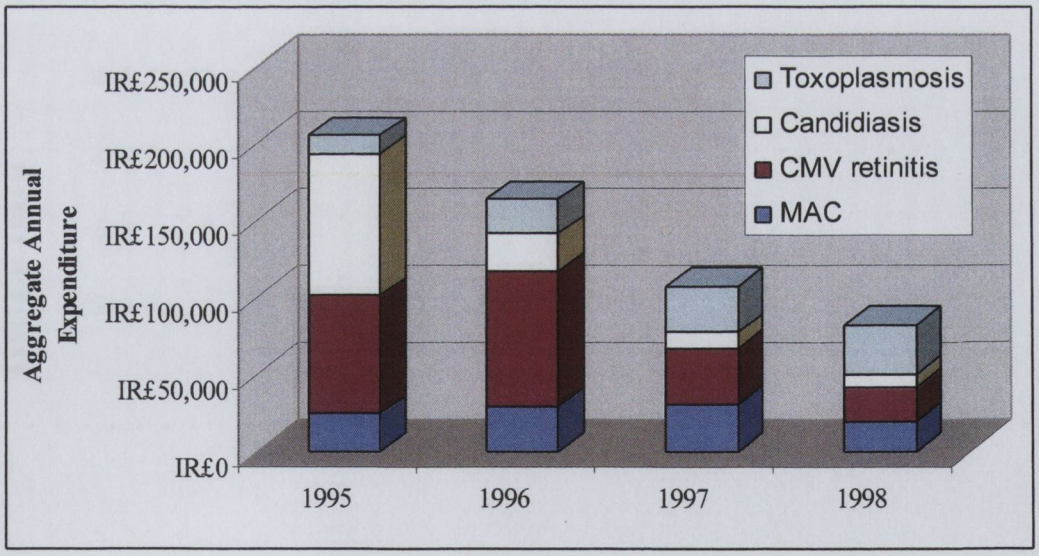


Figure 6.2 Annual aggregate expenditure on outpatient pharmacotherapy of MAC, toxoplasmosis, candidiasis and CMV retinitis from 1995 to 1998.

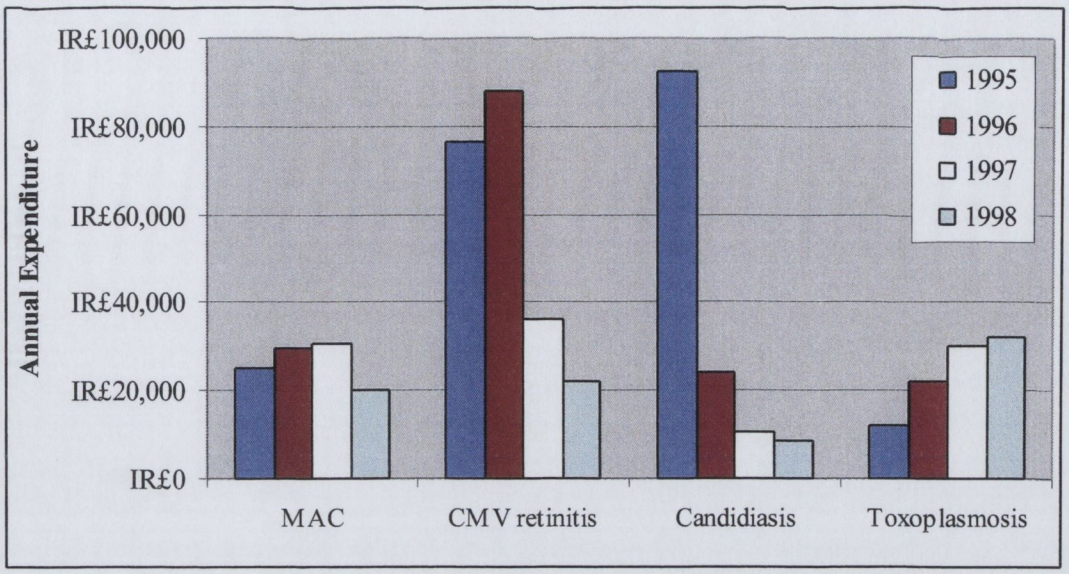


Figure 6.3 Expenditure on outpatient pharmacotherapy of MAC, toxoplasmosis, candidiasis and CMV retinitis each year from 1995 to 1998.

CHAPTER 7

7 THE COST OF INPATIENT CARE FOR HIV-INFECTED INDIVIDUALS

7.1 Introduction:

Drug acquisition cost of HAART is considerably greater than the cost of previous dual and monotherapy regimes. It has been suggested that increased expenditure on HAART might be offset to some extent by decreased expenditure on agents for prophylaxis and treatment of opportunistic illnesses and by cost savings associated with a decreased hospital admission rate [131]. Expenditure on medication can be accurately quantified using dispensed reports from Cliniscript®, the software package used in the satellite pharmacy. A 59.7% decrease between 1995 and 1998 in the outpatient cost of treating four opportunistic infections (MAC, toxoplasmosis, CMV retinitis and oropharnygeal and oesophageal candidiasis) has been noted (Figure 6.2) Calculating the cost savings associated with a decreased admission rate was hampered however, by the dearth of readily available accurate and detailed cost data for any type of admission to an Irish hospital.

The availability of detailed cost of care information for HIV-related admissions would contribute to an evaluation of the pharmacoeconomic impact of HAART in the Irish setting. Categorising cost information by diagnosis and patient characteristics would enhance the utility of the data and allow for its application in the evaluation of cost effectiveness of new therapeutic interventions in the future. Furthermore the cost of care data could be used to validate the casemix method presently employed by the Department of Health to assign a proportion of a hospital's budget based on the complexity of its caseload.

7.2 Aim

The aim of this chapter was to conduct a cost of care study to determine the cost of hospitalisation of HIV-infected individuals in an Irish teaching hospital. It was considered useful to categorise cost of care data according to discharge diagnosis and patient clinical

data. Therefore, it was decided to determine admission costs for HIV and non HIV-related diagnoses as well as costs for patients categorised according to baseline CD4 cell count at admission.

7.3 Method:

7.3.1 Patients admitted, mode of referral, wards, discharge diagnoses

All patients in our cohort who were hospitalised at St. James's Hospital between the first day of January 1999 and the last day of March 1999 were identified using HIPE (Hospital In-Patient Enquiry), the hospital's computerised admission database. If a patient's admission commenced prior to the first day of the study period or if a patient was discharged from hospital subsequent to the date of study closure, data pertaining to the entire admission was included in the final analysis. Patient medical records were reviewed and the following information was abstracted: patient demographics, mode of referral, ambulance transportation, discharge diagnoses, length of stay on specific wards, medical and paramedical consultations and diagnostic tests. The patient drug prescription charts were examined and details of all medication administered to the patient during hospitalisation were noted including specific agents administered, dosage regimens, route of administration, number of dosage units, reconstitution fluids and diluents where appropriate. Details of all laboratory investigations were abstracted from the hospital laboratory administration database.

7.3.2 Constituent costs of inpatient care

Costs were calculated from the perspective of the health service provider; non-direct healthcare costs and intangible costs were excluded from this analysis. A total costing approach was taken in attempt to capture total resource consumption associated with each admission. Admission costs were categorised as follows: ward costs, pharmacy acquisition costs, laboratory investigations, investigative procedures, and supply of blood products.

Ward costs include the baseline cost of admission to each ward as described below, the cost of medical and paramedical staff and transportation via ambulance. Pharmacy acquisition costs include medication and nutrition products such as enteral feeding and total parenteral nutrition. Laboratory investigations encompass biochemistry, haematology, immunology, microbiology, virology, cytology and histology tests. Investigative procedures include diagnostic imaging tests, endoscopic procedures and cardiac investigations such as electrocardiography and echocardiography. Blood products supplied to inpatients include platelets, fresh frozen plasma, red cell concentrate and in the case of haemophiliac patients, cryoprecipitate containing deficient clotting factors.

Ward costs

The mean baseline cost per inpatient bed day in each specific ward was available from the hospital finance department. This baseline cost included staff costs such as nursing and allied staff, administration, catering and other staff, and non staff costs such as expenditure on medical, surgical and other consumables, paramedical support costs, hotel costs such as catering, maintenance, power supply etc., and general administration. This figure was calculated by dividing the total cost of providing these services to a specific ward in 1998 by the number of inpatient bed days during that year. Expenditure on consumables for a specific ward was consistent with quantities supplied to that ward during 1998. Other non-pay costs were calculated as that percentage of total hospital expenditure on these items for 1998, which reflected the proportion of the total square footage of the hospital that that ward occupied. Following a year on year analysis of trends in expenditure in consultation with the hospital finance department, it was decided to apply a 2% per annum and 4% per annum rate of inflation to 1998 non-pay and pay costs respectively to give a mean baseline cost per bed day for 1999. For each inpatient admission, the product of the number of inpatient bed days on each specific ward and the relevant mean baseline cost per day was calculated. All other costs, which included medical care, paramedical care, medication,

laboratory tests, diagnostic imaging and other procedures and blood products, were calculated for each admission on an individual patient basis.

Cost of dedicated multidisciplinary team

The cost of health care professionals who are included in the multidisciplinary team dedicated to our service was calculated as follows. This team which includes medical staff, pharmacists, a clinical nutritionist and medical social workers provides care to HIV-infected inpatients and outpatients as described earlier and also provides outpatient care and occasionally inpatient care to patients with other sexually transmitted diseases. Each member of the team was asked to assign a proportion to the time spent in the care of HIV-infected inpatients. The cost of care of inpatients was calculated as that proportion of the relevant salary inclusive of the employer's contribution to social insurance and divided by the total number of inpatient days to provide a cost per day. Consultations by other medical and paramedical staff, for example psychiatry, physiotherapy etc. were calculated on an hour per consultation basis.

Pharmacy costs

A number of assumptions were made in the estimation of the pharmacy acquisition costs attributed to individual admissions. Current medication costs were taken from the Medical Index of Medical Specialities (MIMS) June 1999. St. James's Hospital operates a generic substitution policy and therefore for any drug available as a proprietary and generic preparation, the cost price of the least expensive generic preparation available was used for the purposes of this analysis. Prices for any drugs not included in MIMS, for example agents available on an unlicensed basis and agents available through hospitals only which includes all antiretroviral drugs were obtained from the pharmacy department at St. James's hospital.

Specific assumption with regard to medication supply included the following:

- for inhalers, creams and eye preparations the cost of the multi-dose preparation was included
- provision of eye drops was calculated as a new preparation dispensed every 7 days in accordance with hospital policy
- although the hospital pharmacy department receives various discounts from wholesalers on the basis of bulk purchase, these are often negotiated on an individual basis and were therefore not included in this analysis

Expenditure on intravenous drugs included the cost of reconstitution and dilution fluids where appropriate. All intravenous drugs and topical preparations are subject to value added taxation (VAT) at a rate of 21% which was included.

Laboratory tests, blood products, investigative procedures

Cost of laboratory tests, blood products and clinical procedures including diagnostic imaging, endoscopy etc. was calculated as the product of the number of investigations or blood product units and the individual cost of each. These costs were obtained from the relevant hospital directorates and are consistent with prices charged to outside consumers. The cost of ambulance transportation was obtained from the company contracted to provide an ambulance service to St. James's Hospital.

The overall cost of all admissions included in this assessment was computed as the aggregate of the sum of costs assigned to individual admissions and the product of the baseline average cost per bed day and the number of inpatient bed days in specific wards as described earlier. Therefore the mean cost per admission and the mean cost per inpatient bed day was determined.

7.3.3 Admissions according to discharge diagnosis and baseline CD4 cell count.

Admissions were classified according to whether the discharge diagnosis was HIV-related or not, according to the stage of disease experienced by the patient (1993 CDC classification of HIV disease) [10] and according to the patient's CD4 cell count on admission. CD4 cell counts were categorised as follows: less than 50 x 10^6/L, 50 to 200 x 10^6/L and greater than 200 x 10^6/L. The mean cost per admission and per inpatient day was calculated for HIV and non HIV-related admissions, for patients in each stage of HIV disease and for each CD4 cell count classification.

7.3.4 Admissions according to Diagnosis Related Group classification

In accordance with the casemix model, all hospital admissions are assigned a Diagnosis Related Group classification (DRG) in order to facilitate the operation of a prospective payment system whereby a proportion of each hospital's budget is determined by the complexity of its casemix load. The DRGs assigned to each of the admissions included in this assessment were obtained from the hospital coding department and therefore the total cost of all admissions was estimated using the casemix model. The admission cost for each DRG as determined by the microcosting approach in our assessment was compared to the casemix model estimations of admission cost on which a proportion of the hospital's future allocation of resources will be based.

7.4 Results

7.4.1 Patients admitted, mode of referral, wards, discharge diagnoses.

Sixty-nine admissions were included in the assessment resulting in 1037 inpatient days. The mean length of stay was 15 days with a range of 1 to 65 days. Patient demographics are summarised in Table 7.1. The median age of patients admitted was 35.6 years (range 22.1 to 58.6 years). There were twice as many male as female patients and the most

Table 7.1: Baseline characteristics of HIV-infected individuals admitted during the first three months of 1999.

Patients admitted*:	69
Patient age (years):	
Median	35.6
Range	(22.1-58.6)
Gender:	
Male	48 (69.6%)
Female	21 (30.4%)
Risk factor for acquisition of HIV:	
Intravenous drug use	38 (55.1%)
Homosexual	19 (27.5%)
Heterosexual	11 (15.9%)
Haemophiliac	1 (1.5%)
CDC 1993 Classification of HIV disease:	
Stage A	1 (1.4%)
Stage B	2 (2.9%)
Stage C	66 (95.7%)
CD4 cell count on admission:	
$< 50 \times 10^6/L$	29 (42.0%)
$50\text{-}200 \times 10^6/L$	19 (27.5%)
$> 200 \times 10^6/L$	21 (30.5%)

*Patients may have been admitted more than once during the study period.

common risk factor for acquisition of HIV infection amongst those admitted was intravenous drug use (55.1%). In 95.7% of cases, patients had progressed to Stage C of HIV disease. Two patients were categorised as Stage B disease and one patient as Stage A disease by the 1993 CDC classification of HIV disease. According to the CD4 cell count classification adopted for this study, 42.0% of patients admitted had CD4 cell counts less than 50 x 10^6/L, 27.5% had CD4 cell counts between 50 and 200 x 10^6/L whilst 30.5% had CD4 cell counts greater than 200 x 10^6/L.

A third of patients were admitted via the accident and emergency department whilst 49.3% were admitted following an outpatient attendance at either the HIV outpatient clinic or day ward (Table 7.2). The remainder constituted either elective admissions or transfers from other hospitals, which do not have a specialist HIV service. Five patients (7.2%) died following hospitalisation. 91.3% of patients included in the study were admitted to the HIV specialist medical ward accounting for 84.6% of all inpatient days. One patient spent time in the coronary care unit following an overdose and two patients were admitted to the high-dependency unit during the course of their admissions. 36.2% of patients were admitted to other wards in the hospital and subsequently transferred to the HIV specialist medical ward.

HIV-related indications accounted for 75.4% of discharge diagnoses and included admissions for the treatment of opportunistic diseases such as tuberculosis, non-Hodgkin's lymphoma and respiratory tract infection in addition to hospitalisation for the management of adverse drug reactions. The remaining discharge diagnoses (24.6%) were non HIV-related and included management of hepatitis B and C, and management of the complications of intravenous drug use such as skin abscess and deep venous thromboses. Details of the discharge diagnoses of admissions included in the study are summarised in Table 7.3.

Table 7.2: Details of admissions of HIV-infected individuals in the first three months of 1999 including: number of inpatients days, mean length of stay, referral source for admission, mortality, and ward occupancy.

Admissions:		69
Inpatient days:		1037
Length of stay (days):	*Mean*	15.0
	Range	(1-65)
Source of referral for admission:		
	Accident & Emergency	23 (33.3%)
	HIV Outpatient Clinic	34 (49.3%)
	Elective admissions	9 (13.0%)
	Transfers from other hospitals	3 (4.3%)
Patients who died during admission:		5 (7.2%)
Specialist HIV medical ward:		
	*Patients admitted**	63 (91.3%)
	Inpatient days	877 (84.6%)
High Dependency & Coronary Care Units:		
	*Patients admitted**	3 (4.3%)
	Inpatient days	11 (1.1%)
Other Wards:		
	*Patients admitted**	25 (36.2%)
	Inpatient days	149 (14.4%)

*Patients may have been admitted to more than one ward during the course of a single admission.

Table 7.3: Discharge diagnoses of HIV-infected individuals hospitalised during the first three months of 1999.

Discharge diagnosis	Number of admissions
HIV related:	(75.4%)
Respiratory tract infection	19
Malignancy	12
Adverse drug reactions	5
Mycobacterium tuberculosis	3
Cryptococcal meningitis	3
Progressive multifocal leucoencephalopathy	2
Pneumocystis carnii pneumonia	2
Infection	2
Oesophageal candidiasis	1
HIV related wasting	1
HIV related skin disease	1
Cytomegalovirus	1
Non-HIV related:	(24.6%)
Intravenous drug use	7
Infection	5
Infective hepatitis	3
Other	2

7.4.2 Constituent costs of inpatient care

The total cost of inpatient care for patients included in this study was IR£372,738 resulting in a mean cost per admission of IR£5,402 and a mean cost per inpatient day of IR£359. Costs attributed to each of the constituent categories are summarised in Table 7.4. Ward based costs accounted for the majority of the total cost of inpatient care (58.5%). The remaining expenditure was attributable to pharmacy acquisition costs (14.5%), laboratory tests (12.1%), blood products (10.2%) and investigative procedures (4.7%). Nursing and allied staff accounted for the majority of ward-based costs (55.6%). The largest proportion of laboratory investigations was attributed to microbiology and virology (36.8%) while diagnostic imaging accounted for the majority of procedure costs (77.2%). Anti-infectives including antibiotics, antifungals, antiretrovirals and other antivirals accounted for 72% of pharmacy acquisition costs. Of patients admitted, 97% were prescribed at least one anti-infective agent but HAART was only prescribed for 32.1% of inpatient days. (Figure 7.1) Cytotoxic chemotherapy accounted for only 2.4% of medication costs, while 10.8% was attributed to management of blood dyscrasias and 3.3% to psychotropic medication. Nutrition products including enteral feeding, total parenteral nutrition and vitamin supplementation accounted for 5.6% of total expenditure on pharmaceuticals.

Table 7.4: Hospitalisation costs for 69 HIV-infected individuals admitted during the first three months of 1999.

Total Cost:		**IR£372,738**	
Ward costs:	**(58.5%)**	**IR£217,959**	
Nursing & allied staff		IR£121,230	(55.6%)
Medical & paramedical staff		IR£35,108	(16.1%)
Medical, surgical & other consumables		IR£12,169	(5.6%)
Ambulance transport		IR£845	(0.4%)
Other overheads		IR£48,607	(22.3%)
Pharmacy acquisition costs:	**(14.5%)**	**IR£53,903**	
Laboratory costs:	**(12.1%)**	**IR£45,148**	
Microbiology & virology		IR£16,616	(36.8%)
Biochemistry		IR£13,764	(30.5%)
Haematology		IR£9,123	(20.2%)
Immunology		IR£4,026	(8.9%)
Histopathology & cytology		IR£1619	(3.6%)
Investigative procedure costs:	**(4.7%)**	**IR£17,638**	
Diagnostic imaging		IR£13,609	(77.2%)
Other procedures		IR£4,029	(22.8%)
Blood products costs:	**(10.2%)**	**IR£38,090**	

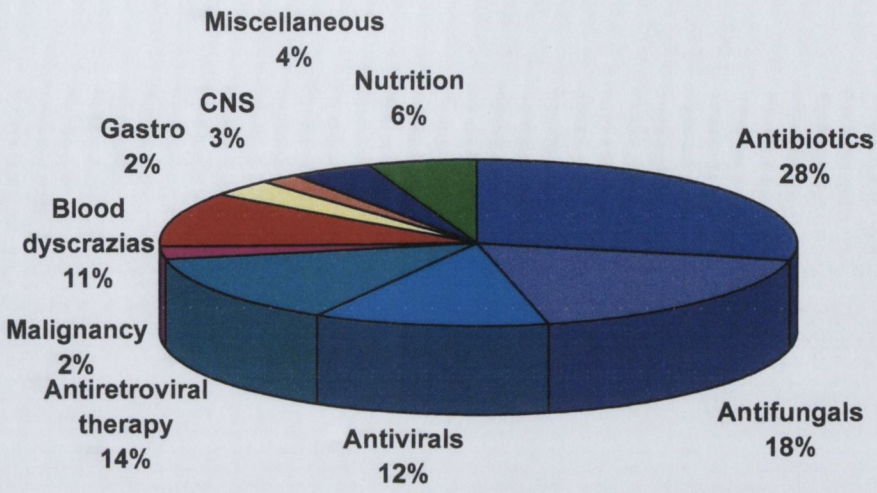


Figure 7.1 Expenditure on pharmacotherapy for 69 HIV-infected patients according to therapeutic classification.

7.4.3 Admissions according to discharge diagnosis and baseline CD4 cell count.

The cost per admission, cost per inpatient day and details of hospitalisation costs for HIV-related and non HIV-related admissions and for admissions classified according to CD4 cell count at admission are summarised in Tables 7.5, 7.6 and 7.7. The majority of admissions included in this study had HIV-related discharge diagnoses. HIV-related admissions although associated with a less expensive cost per inpatient day were characterised by a longer mean length of stay and therefore a more expensive cost per admission than non HIV-related admissions. There was an inverse relationship between CD4 cell count on admission and both the cost per inpatient day and the cost per hospital admission. For each type of admission examined, ward based costs accounted for the majority of the constituent costs of inpatient care.

Table 7.5: Hospitalisation costs expressed per admission and per inpatient day for HIV-infected individuals admitted in the first three months of 1999 according to discharge diagnosis and according to CD4 cell count on admission.

		Cost per admission	Cost per inpatient day
All admissions:	*Mean*	IR£5,402	IR£359
	Range	[IR£256-IR£41,469]	[IR£128-IR£1674]
Discharge diagnosis:			
HIV related:	*Mean*	IR£5,791	IR£346
	Range	[IR£282-IR£41,469]	[IR£218-IR£1674]
Non-HIV related:	*Mean*	IR£4,211	IR£426
	Range	[IR£256-IR£28,094]	[IR£128-IR£877]
CD4 cell count on admission:			
< 50 x 10^6/L	*Mean*	IR£6,444	IR£389
	Range	[IR£1005-IR£41,469]	[IR£250-IR£1674]
50-200 x 10^6/L	*Mean*	IR£5,154	IR£358
	Range	[IR£1,072-IR£28,094]	[IR£218-IR£877]
> 200 x 10^6/L	*Mean*	IR£4,138	IR£309
	Range	[IR£256-IR£14,755]	[IR£128-IR£455]

Table 7.6: Details of admission costs for HIV-infected patients admitted during the first three months of 1999 according to discharge diagnosis.

		HIV-related diagnosis	Non-HIV related diagnosis
Number of admissions:		52	17
Number of inpatient days:		869	168
Length of stay (days):	*Mean*	16.7	9.9
	Range	[1-65]	[1-40]
Cost per admission:		IR£5,791	IR£4,211
Mean constituent costs per admission:			
Ward		IR£3,472 (60.0%)	IR£2199 (52.2%)
Pharmacy		IR£922 (15.9%)	IR£347 (8.3%)
Laboratory		IR£695 (12.0%)	IR£531 (12.6%)
Investigative procedures		IR£251 (4.3%)	IR£272 (6.5%)
Blood products		IR£451 (7.8%)	IR£860 (20.4%)

Table7.7: Details of admission costs for HIV-infected patients admitted during the first three months of 1999 according to CD4 cell count on admission.

CD4 cell count on admission		**< 50 x 10^6/L**	**50-200 x 10^6/L**	**> 200 x 10^6/L**
Number of admissions:		29	20	20
Number of inpatient days:		481	288	268
Length of stay (days):	*Mean*	16.6	14.2	13.4
	Range	[1-53]	[2-49]	[1-65]
Cost per admission:		IR£6,444	IR£5,154	IR£4,138
Constituent costs per admission:				
Ward		IR£3,587 (55.7%)	IR£3062 (59.4%)	IR£2635 (63.6%)
Pharmacy		IR£1,267 (19.7%)	IR£375 (7.3%)	IR£483 (11.7%)
Laboratory		IR£690 (10.7%)	IR£628 (12.2%)	IR£628 (15.2%)
Investigative procedures		IR£234 (3.6%)	IR£239 (4.6%)	IR£302 (7.3%)
Blood products		IR£664 (10.3%)	IR£851 (16.5%)	IR£90 (2.2%)

7.4.4 Admissions according to Diagnosis Related Group classification

The DRG classifications assigned to the admissions included in this study are summarised in Table 7.8. Thirty-one admissions were assigned one of the HIV disease specific DRGs. Thirteen were coded as 489 i.e. HIV disease with a major related condition and 18 were coded as 490 i.e. HIV disease with or without other related condition. No admission was coded as the remaining HIV disease specific DRG 488 i.e. HIV disease with extensive operative procedure. Code 101 and code 102, which refer to other respiratory diagnosis with or without complicating condition accounted for 8 and 4 admissions respectively. A variety of other DRGs were assigned to the remaining admissions. The mean cost of the HIV disease specific DRG admissions i.e. DRG 489 and 490 as calculated in this study was IR£4,922 and IR£3,676 i.e. 25% and 50% greater than the DRG derived estimation of the cost of an admission. Furthermore, the respiratory disease related DRGs cost 148% and 288% more by the microcosting method than by the DRG method. The cost of the admissions assigned other DRGs varied from 32% to 718% more than the DRG estimated cost with the exception of two admissions for which the measured cost in this study was 14% and 56% less than the estimated DRG cost respectively. As a consequence of these differences between the measured and the estimated cost of care for specific admissions, the total cost of inpatient care for the 69 admissions included in this study as estimated by the DRG method was IR£159,047 whereas the total cost calculated by this microcosting study was 2.34 times more at IR£372,731.

Table 7.8: Details of the Diagnosis Related Group (DRG) codes which were assigned to HIV-infected patient admissions during the first three months of 1999, the estimated value according to the casemix model and the mean value as measured by the microcosting study.

DRG code	Details of diagnosis	Number of admissions	Estimated value (IR£)	Mean measured value (IR£)
489	HIV with major related condition	13	3,941.01	4,922.65
490	HIV with/without other related condition	18	2,459.00	3,676.48
101	Other respiratory diagnosis with complicating condition	8	1,745.59	4,331.45
102	Other respiratory diagnosis without complicating condition	4	958.22	3721.86
100	Respiratory signs +symptoms without complicating condition	1	645.81	911.57
12	Degenerative nervous system disorder	1	2,841.12	11,244.86
25	Seizure + headache, >17 years, with complicating condition	2	944.28	7724.69
79	Respiratory infections+ inflammations, age>17	1	3,912.12	11474.37
89	Simple pneumonia+pleurisy with complicating condition, age>17	1	2,235.73	977.12
182	Oesophagitis, gastroenteritis +miscellaneous digestive disease, age>#	2	1,418.18	5534.61
183	Oesophagitis, gastroenteritis +miscellaneous digestive disease, age>#	3	804.31	2889.50
205	Disorders of liver excluding malignancy, cirrhosis, alcoholic hepatitis with complicating condition	2	2,448.41	2,102.93
206	Disorders of liver excluding malignancy, cirrhosis, alcoholic hepatitis without complicating condition	1	1,027.76	1645.32
278	Cellulitis, age > 17 without complicating condition	1	979.40	1296.05
284	Minor skin disorders without complicating condition	2	645.64	4886.14
394	Other blood disorder	1	2,801.23	7381.15
397	Coagulation disorders	1	2349.92	14755.86
403	Lymphoma or leukaemia with complicating condition	2	3,429.22	24380.55
420	Fever of unknown origin, age>17 without complicating condition	1	1,210.97	3022.85
423	Other infections+parasitic diseases	1	2,328.92	13689.45
174	Gastrointestinal haemorrhage with complicating condition	1	1,991.10	28,094.64
188	Other digestive system diagnoses, age > 17 with complicating condition	1	1,952.09	345.12
185	Dental + oral disease excluding extraction and restorations	1	1,306.28	256.42
	Total Cost	**69**	**159,046.60**	**372,731.27**

7.5 Discussion

7.5.1 Patients admitted, mode of referral, wards, discharge diagnoses

The patients included in this study share a number of demographic characteristics with HIV-infected individuals hospitalised at our centre from the beginning of 1995 to June 1999 (Table 2.6). The majority of patients admitted were male, had acquired HIV through intravenous drug use and had already progressed to stage C disease.

Wards to which HIV-infected patients were admitted during the study included the HIV specialist medical ward, other medical wards, the coronary care unit and the high dependency unit. The coronary care unit provides a high intensity of care while the high dependency unit, which provides an intermediate intensity of care often acts as a step down facility between the intensive or coronary care units and the general medical wards. The majority of patients (91.3%) were either admitted directly or ultimately transferred to the HIV specialist medical ward thereby accounting for the majority of inpatient days (84.6%). Three patients were admitted to either the coronary care or the high dependency unit. These wards are associated with high ward-based costs compared to the medical wards as a consequence of intensive staffing levels. However since these 3 admissions accounted for only 1.1% of the total inpatient days, the impact of the increased cost per bed day associated with these wards was not substantial. The remainder of inpatient bed days was spent on other medical wards including 8.5% of bed days on private wards. Of note the private wards are associated with ward-based costs similar to or less than the specialist HIV medical ward.

The HIV specialist team provides inpatient care for HIV-infected individuals admitted for HIV and non HIV-related indications. 75.4% of admissions in this study were HIV-related as were the majority of all admissions between January 1995 and June 1999 (Table 2.7). The most common reasons for HIV-related admissions included respiratory tract infection,

management of HIV-related malignancies such as non-Hodgkin's lymphoma and management of adverse drug reactions to HIV-related medication. Management of adverse drug reactions accounted for 101 inpatient days or 9.7% of the total number of inpatient days. An admission for the management of hepatitis associated with the antiretroviral agent nevirapine accounted for the admission of longest duration in the study i.e. 65 days. Therefore it appears that medication used to treat HIV infection and HIV-related disease is associated with considerable patient morbidity and substantial hospitalisation related expense. Complications of intravenous drug use accounted for the largest proportion of non HIV-related admissions (41.2%) as the majority of patients included in the study acquired HIV infection via this route. Many HIV-infected patients in our cohort are co-infected with either hepatitis B or hepatitis C or both. Therefore, a notable proportion (17.6%) of non HIV-related admissions were attributed to complications secondary to infective hepatitis.

7.5.2 Constituent costs of inpatient care.

Ward costs

The mean cost per hospital admission of an HIV-infected individual as determined in this study was IR£5,402 and the mean cost per inpatient day was IR£359. Similar to findings in other cost of care studies, ward based costs accounted for the majority of inpatient expense (58.5%). Not surprisingly, nursing and allied staff accounted for a substantial proportion (55.6%) of ward-based costs. It is well recognised that staff salaries constitute a major proportion of hospital expenditure (76% of the 1998 budget at St. James's Hospital) [132]. Inpatients receive 24-hour attention from nursing and allied staff in contrast to medical and paramedical staff who with the exception of the on-call team are available during daytime working hours only. The "other overheads" category which accounted for a substantial 22.3% of ward based costs includes administration, catering, domestic and maintenance staff in addition to non-pay costs such as paramedical support, general administration and

hotel costs including catering, power supply, maintenance etc. Ward-based costs vary little between the HIV specialist medical ward and the other medical wards. These wards accounted for 98.9% of inpatient days; therefore cost per inpatient day varied little between admission. Any variation in ward-based costs between admissions could be attributed directly to duration of inpatient admission.

Pharmacy costs

Pharmacy acquisition costs represented 14.5% of total inpatient expenditure during the study period. Not surprisingly anti-infective agents accounted for the majority of expenditure on pharmaceuticals (72.0%). Antiretroviral therapy although only prescribed during less than half of the inpatient days, resulted in 13.6% of total drug expenditure due to the high acquisition cost of HAART at approximately IR£15 to IR£20 per day. The proportion of inpatient days prescribed HAART (32.1%) is less than the uptake of HAART in the cohort as a whole (57%) for the first three months of 1999 despite the fact that only 2 inpatients had CD4 cell counts in excess of the threshold for initiation of antiretroviral therapy i.e. $> 350 \times 10^6$/L. There are a number of reasons for this. Some patients were admitted to hospital at time of diagnosis of HIV disease and therefore had not yet had the opportunity to commence HAART. A number of patients (7.2%) were admitted for management of adverse drug reactions to HAART constituents and therefore had antiretroviral therapy suspended pending resolution of their symptoms. Five patients died during the study and antiretroviral therapy and other active interventions were suspended in the terminal phase of the admission immediately prior to death. The majority of patients admitted during the study acquired HIV infection through intravenous drug use. In Ireland, this risk group might be considered less likely than other transmission groups to be prescribed antiretroviral therapy because of factors contributing to poor compliance such as chaotic lifestyle, poor socio-economic circumstances and lack of post primary education. However, on closer analysis of the data, there was no association between

intravenous drug use and the likelihood of not receiving HAART for inpatients included in this study (data not shown).

High expenditure on other anti-infectives can be attributed to high cost antibiotics such as teicoplanin, pipericillin/tazobactam etc., antifungals such as the azoles and the expensive liposomal formulation of amphotericin and antivirals such as intravenous acyclovir and ganciclovir. All but two of the patients were prescribed at least one anti-infective agent during admission thereby explaining why the majority of pharmaceutical expenditure was attributed to this pharmacological class. Although 12 of 69 admissions were for management of HIV-related non-Hodgkin's lymphoma, cytotoxic therapy was only administered during three of those admissions and subsequently only accounted for 2.4% of total drug expenditure. Management of blood dyscrasias accounted for 10.8% of pharmacy acquisition costs. The majority of this expenditure was accounted for by the use of granulocyte colony stimulating factor to ameliorate chemotherapy-induced neutropenia. Nutrition products accounted for 5.6% of total drug expenditure, the majority of which was attributed to the provision of high cost total parenteral nutrition for just one patient.

Laboratory costs

Laboratory investigations accounted for 12.1% of the total cost of inpatient care in this study. Not surprisingly, microbiology and virology accounted for the largest proportion of expenditure on laboratory tests. Biochemistry and haematology investigations also accounted for substantial laboratory expenditure as these investigations are frequently required to monitor not only the effect of the disease process but also of the medications used in patient management. Immunology investigations accounted for 8.9% of total expenditure on laboratory tests. CD4 cell count estimation as a surrogate marker of HIV disease progression and consequent susceptibility to opportunistic infection accounted for the majority of immunological investigations.

Blood product costs

Supply of blood products accounted for 10.2% of total expenditure on inpatient care. A total of 16 patients received blood products during the course of their admission. The high acquisition cost per unit explains substantial expenditure on these items. In fact a single patient with fulminant hepatic failure due to co-infection with hepatitis C accounted for 37.5% of total expenditure on blood products.

Investigative procedure costs

Of interest, 4.7% of total expenditure was attributed to investigative procedures. The majority (77.2%) was accounted for by diagnostic imaging including X-ray, computerised tomography (CT) and ultrasound examinations. The most expensive diagnostic imaging investigation included in this study i.e. magnetic resonance imaging (MRI) was conducted on a total of 9 patients included in the study. Other procedures included gastroscopies, bronchoscopies, electrocardiographs and pulmonary function tests.

7.5.3 Admissions according to HIV-related and non HIV-related diagnoses

On classifying admissions as HIV-related or not, it was noted that although the cost per inpatient day for non HIV-related admissions was considerably more than that of HIV-related admissions (18.7%), the total cost of a HIV-related admission exceeded the cost of a non HIV-related admission by 27.3%. Examination of the constituent inpatient costs and their determinants may explain this finding. Ward based costs account for the majority of inpatient expense. As discussed earlier, there is very little variation in the cost per inpatient bed day for the wards that account for the great majority (98.9%) of inpatient days in this study. Therefore, the increased cost per HIV-related admission compared to non-HIV related admissions is a reflection of the greater mean length of stay. The greater mean length of stay for HIV-related admissions may be explained by the fact that most of these admissions were for AIDS defining illnesses, which by definition are associated with

considerable morbidity and prolonged inpatient care. Pharmacy costs were considerably greater for HIV-related versus non HIV-related admissions. The high drug acquisition cost of many of the agents used to treat AIDS defining illnesses, for example liposomal amphotericin, ganciclovir, granulocyte colony stimulating factor etc. accounts for the increased pharmacy expenditure associated with HIV-related admissions. The mean cost of laboratory investigations per admission was also greater in HIV-related admissions. By contrast expenditure on other diagnostic procedures was marginally greater per admission for non HIV-related admissions and there was a two-fold increase in the mean cost of blood products per admission for non HIV-related versus HIV-related admissions.

7.5.4 Admissions according to CD4 cell count at baseline

Admission costs were also classified according to the patient's CD4 cell count at admission. An inverse relationship between CD4 cell counts at admission and both cost per inpatient day and cost per admission was noted. The CD4 cell count is used as a surrogate marker of HIV disease progression [24, 27]. As HIV disease progresses, CD4 cell counts decline reflecting progressive immunosuppression and resulting in an increased susceptibility to opportunistic infection. Therefore it may be predicted that as CD4 cell count declines, patient morbidity increases and therefore hospitalisation costs increase. The mean length of stay for patients with CD4 cell count $<50 \times 10^6$/L and between 50 and 200 $\times 10^6$/L was considerably longer at 16.6 and 15.2 days respectively than the mean length of stay in patients with higher CD4 cell counts greater than 200 $\times 10^6$/L i.e. 12.8 days. Mean cost per admission reflected this trend with the mean cost per admission for patients in the lowest CD4 cell count category amounting to IR£6,444 decreasing to IR£5,154 and IR£4,138 as CD4 cell count increased to between 50 and 200 $\times 10^6$/L and to greater than 200 $\times 10^6$/L respectively.

Ward based costs again accounted for the majority of hospitalisation costs in each category and were considerably less expensive per admission for patients with a CD4 cell count > 200 x 10^6/L. Pharmacy costs per admission were much greater for patients with CD4 cell count on admission < 50 x 10^6/L. The risk of many opportunistic infections increases substantially as CD4 cell count decreases below 50 x 10^6/L and pharmacotherapy of many opportunistic infections is associated with high drug acquisition costs. Expenditure on laboratory investigations per admission was also greater for patients with baseline CD4 cell count < 50 x 10^6/L. While an inverse relationship between CD4 count and ward, pharmacy and laboratory costs was noted, costs of investigative procedures actually increased with CD4 cell count but accounted for a small proportion of the overall cost of an admission. Expenditure on blood products was considerably higher for patients whose CD4 cell count was < 200 x 10^6/L compared to patients with CD4 >200 x 10^6/L. The likelihood of either HIV-related bone marrow suppression or a requirement for bone marrow toxic medication, for example ganciclovir, high dose zidovudine to treat HIV-related dementia etc. increases as the CD4 cell count declines thus explaining the trend observed in expenditure on blood products.

7.5.5 Admissions according to Diagnosis Related Group classification.

Since 1993, reimbursement for acute hospitals in Ireland has been in part influenced by relative case mix complexity of patients treated [39]. This system is based on the casemix model's assignment of a relative value to hospital admissions according to DRG classification. The relative value is based on costing data derived from US hospitals with some modifications for costs within the Irish system. A monetary value is assigned to the cost of a baseline admission whose relative value is 1.0 by the Department of Health Speciality Costing Program. The monetary value varies according to the specific hospital's classification, for example St James's as the largest university teaching hospital in the country is classified as a Group 1 hospital and therefore is associated with the highest

monetary value for baseline admission costs. Therefore, the cost of any admission can be estimated as the product of the relative value of its assigned DRG and the baseline admission cost. In the absence of an accounting system, which would allow itemisation of resource use by patient, the DRG system provides an alternative to individual data collection for the assignment of a proportion of a hospital's budget based on the complexity of its casemix.

There are 3 DRGs specifically assigned to HIV disease admissions (1) DRG 488: HIV with extensive operative procedure, (2) DRG 489: HIV with major related condition and (3) DRG 490: HIV with or without other related condition. However admissions of HIV-infected individuals may be assigned a DRG other than one of the three HIV-related diagnoses. In this study only 31 of the 69 admissions were assigned HIV-related DRGs and no admission was coded as DRG 488 i.e. the DRG associated with the highest relative value for HIV disease. Each admission is assigned a DRG code by the hospital coding department based on a standardised assessment of data extracted from the discharge summary in the medical chart. An admission may be assigned an alternative DRG as a primary diagnosis and one of the HIV-related DRGs, as a secondary diagnosis if it is considered that the alternative DRG more accurately reflects resource consumption. For example, an HIV-infected patient admitted with a myocardial infarction would be classified as myocardial infarction as primary diagnosis and HIV infection as secondary diagnosis. The hospital's casemix index (CMI), which is the aggregate of the product of the relative value of each primary DRG and the number of cases per DRG divided by the total number of discharge equivalents, is the value on which adjustment of the hospital's future budget allocation is based.

The total cost of all admissions included in this study as determined by the microcosting method was 2.34 times greater than the cost estimated by the casemix model. This finding appears to suggest that the casemix model seriously underestimates the cost of inpatient

care for HIV-infected individuals. This may have grave implications for the hospital concerned as an underestimation of the relative value of DRGs commonly assigned to HIV-infected individuals would result in a reduced casemix index and could potentially result in underfunding of the hospital in the next budget allocation. As the effect of the casemix method is budget neutral amongst the participating hospitals, underestimation of the casemix index as a consequence of falsely low relative values would be inconsequential if all DRGs were undervalued to the same extent. However it has been shown recently that the relative value assigned to other DRGs including congestive cardiac failure is very closely reflective of the true value of these admissions in the Irish healthcare system [133, 134]. This study's findings constitute a cause for concern for any of the tertiary referral centres, which are responsible for the provision of the majority of inpatient care for HIV-infected adults in this country. All of the HIV referral centres are major teaching hospitals, are considered to have similar hospitalisation costs and are therefore grouped together for casemix allocation purposes. The cost of care data generated in this chapter may be considered representative of the national cost of providing inpatient care to HIV-infected patients.

The mean cost of admissions coded as either of two HIV disease specific DRGs was 25% and 50% more than the casemix model estimated cost. Since more than 10 admissions for each of these DRGs were included in the calculation of the mean measured cost of admission, this supports the suggestion that the relative value assigned to these DRGs should be increased. The measured cost of some of the other DRGs was up to 7 fold more than the casemix model estimated cost. However it must be presumed that the casemix estimated value for a DRG represents a mean value which is associated with a range that encompasses cheaper and more expensive admissions for the same indication. The number of each DRG admission other than the HIV specific ones was small i.e. < 10 and it is possible that the admissions included in this study fall at the upper end of the presumed range around the estimated mean relative value. Alternatively some of the discrepancy

between the measured and the estimated cost of admissions may be due to inaccurate assignment of DRG codes.

Assignment of a specific DRG to an admission is based on data entered on the patient's discharge summary. This information is usually recorded by the most junior and frequently the busiest member of the medical team who may not understand the implications of inaccurate information leading to inappropriate assignation of DRG codes. By the author's classification, 52 admissions in this study were for HIV-related indications. Only 31 of these admissions were assigned an HIV disease specific DRG by the hospital coding department. The remaining admissions for the most part were assigned DRGs with relative values less than the HIV disease specific codes. In addition no admission was coded as the most expensive HIV disease specific DRG i.e. code 488. Assigning all HIV-related admissions an HIV disease specific DRG including use of code 488 where appropriate would increase the estimated cost of inpatient care to a figure closer to the measured value.

There also exists potential for inaccuracies in the estimation by the Irish casemix model of the cost associated with specific DRGs. A locally derived system of measuring the actual cost of admissions is preferable but would require a high level of investment. In the absence of a local cost database, calculation of the relative value for specific admissions relies on the service weights for different constituents of care (nursing, laboratory etc.) associated with specific DRGs measured in the US healthcare system subject to some modification for Irish costs by the Department of Health's Speciality Costing Program. In the US, calculation of DRG weights and costs is collected on an individual patient basis (microcosting), whereas in Ireland an administrative system capable of linking resource consumption to particular admissions does not exist. Therefore, adjustment of the US calculated service weights and costs is based on global hospital expenditure on ten different specialities including nursing, theatre, physician care etc. (macrocosting). Other services including pharmacy and laboratory are not included in this Program and are

allocated on the basis of US derived service weights. Contrasting practices in some aspects of healthcare between the US and Ireland, and the different approaches to cost data collection may result in inaccurate estimation of DRG based costs.

Whereas the DRG system was initially designed as an information tool to facilitate the comparison of casemix complexity between hospitals, it now forms the basis of a mechanism for prospective budget allocation. It appears that the calculation of relative values for specific DRGs and the assignment of DRG codes need further refinement. A cost of care project such as this one helps to identify deficiencies in the casemix model system and provides a useful benchmark for refinement of estimations to more accurately reflect actual costs. At present the casemix system may result in adjustment by 15% of the difference between the current budget and the casemix estimation of expenditure up to a maximum of +/- 2.5% of the casemixed proportion of the hospital budget. This rarely results in an adjustment of the total hospital budget by greater than 1%. Refinement of the process will be of even greater consequence in the future when it is anticipated that a larger proportion of the hospital budget will be determined by the casemix system.

Healthcare managers can utilise Irish cost data to more accurately project future expenditure and resource consumption by this cohort. Any such projections should take account of how the cost of inpatient care varies with discharge diagnosis i.e. HIV-related and non HIV-related indications and with baseline CD4 cell counts. Knowledge of the cost of inpatient care and its relevant constituents is necessary for the evaluation of the cost-effectiveness of any new intervention for the management of HIV-infected individuals. Such evaluations can guide budget allocation decisions by clinicians and/or healthcare managers. As illustrated above, ward costs, which are dependent on length of stay, constitute the majority of the admission costs for HIV-infected patients regardless of diagnosis or immunological function. Therefore any intervention which might decrease the length of inpatient stay is likely to have a major impact on the cost of hospitalisation. For

example at present a patient with azole resistant candidiasis frequently requires admission for administration of amphotericin since this agent is administered by the intravenous route, requires close monitoring of renal function and serum electrolytes and requires adjunctive parenteral hydration. The introduction of a new orally active agent for the treatment of azole resistant candidiasis would greatly reduce the duration of inpatient stay and in some cases negate the need for hospitalisation. Prior to the availability of a study such as this, the pharmacoeconomic evaluation of any entity in our healthcare system has necessitated the extrapolation of cost of care from another country most commonly the United Kingdom [135]. However such an approach is fraught with difficulty because of the extent to which healthcare systems and acquisition costs vary between countries. Should a new agent for the management of azole resistant candidiasis become available, information on the cost of inpatient care as generated in this study would be invaluable in the evaluation of the new drug's cost effectiveness in the Irish healthcare setting.

The patient based approach to calculation of costs adopted for this study allows for manipulation of the data to link resource consumption and costs to individual patients, patient groups and specific discharge diagnoses. Therefore this study provides a useful resource for accurately estimating the burden of illness associated with HIV infection and related opportunistic diseases in an ever-changing dynamic cohort. This data is also a prerequisite for the pharmacoeconomic evaluation of new and existing interventions for the management of these indications in the Irish healthcare setting including new pharmacotherapeutic agents and also other therapeutic interventions such as phenotypic resistance assays and immunotherapy, which may become available in the near future.

7.6 Conclusion

In this chapter, an inverse relationship between baseline CD4 cell count and cost of admission was observed. Admissions for HIV-related diagnoses were more expensive than

non HIV-related admissions. In common with other therapeutic areas, the majority of expenditure on inpatient care is attributable to ward cost. Furthermore, this chapter highlights deficiencies in the DRG casemix system of estimating cost of inpatient care, which appears to grossly underestimate actual expenditure.

This chapter represents the first ever detailed evaluation of the cost of inpatient care of HIV-infected patients in Ireland. Such a costing study may prove useful in a number of ways. As mentioned earlier, it has been suggested that the high drug acquisition cost of the constituents of HAART may be partially offset by the decrease in hospitalisation rate which coincided with the adoption of HAART as standard of care antiretroviral therapy. Therefore information on the cost of inpatient care as measured in this study may be extrapolated to assign a monetary value to the observed decrease in admission rate. As in most countries of the world, despite expenditure on methods to prevent transmission of the HIV virus, the incidence rate of HIV infection in Ireland exceeds the mortality rate as described in Chapter 2. The ever-increasing prevalent cohort will place further demands on the healthcare system in the future since cure of HIV infection is unlikely with the current antiretroviral armamentarium and provision of life long HAART is expensive.

CHAPTER 8

8 THE IMPACT OF HAART ON THE COST OF HEALTH CARE FOR HIV-INFECTED INDIVIDUALS IN AN IRISH COHORT.

8.1 Introduction

Several changes in the natural history of HIV infection in the St James's clinic cohort have been demonstrated to date. The number of HIV-infected individuals in the active cohort is increasing as a consequence of an incidence rate in excess of the mortality rate. Intensification and expansion of the criteria for initiation of HAART has coincided with reduced morbidity associated with a decrease in the incidence of opportunistic disease, a reduction in hospital admission rates and an observed decrease in the aggregate cost of pharmacotherapy of four opportunistic infections. Increasing survival is likely to result in a cumulative increase in the cost of providing healthcare to the HIV-infected cohort since the eradication of HIV disease in infected individuals is not likely at least in the near future. Changes in prescribing have resulted in a four-fold increase in outpatient pharmacy expenditure. While it has been suggested that increased outpatient expenditure on pharmaceuticals may have been offset to some extent by savings in other areas of healthcare provision to HIV-infected individuals [131], this hypothesis has not yet been tested in the Irish setting.

8.2 Aim:

The aim of this chapter is to determine the total cost of care for HIV-infected patients attending our service between 1/1/95 and 30/6/99 from the hospital perspective. Therefore, the pharmacoeconomic impact of intensifying antiretroviral therapy strategies can be assessed.

8.3 Method

For this study, a total costing approach was taken to estimate the cost of care provided to HIV-infected individuals from the tertiary healthcare provider perspective. Costs excluded from this study included the following:

- non-direct healthcare costs, for example cost of travelling for a consultation
- indirect costs, for example resources lost such as time lost from work or early retirement
- non tangible costs, for example costs which impact on the patient's quality of life such as pain and suffering

Total cost of care may be subdivided into cost of inpatient care and cost of outpatient care which includes attendance at outpatient clinics and at the day ward.

8.3.1 Cost of inpatient care:

All admissions of HIV-infected individuals between 1/1/99 and 31/3/99 were included in a microcosting evaluation of the cost of inpatient care (Chapter 7). Therefore the mean cost of an inpatient bed day stratified according to the patient's baseline CD4 cell count at admission was calculated. Expenditure on inpatient care each year was computed by linking the cost per day for each CD4 cell count stratum and the number of inpatient days assigned to that stratum. The number of inpatient days assigned to each CD4 cell count stratum each year was extracted from the recently constructed database referred to in Chapter 2. Costs per bed day provided by the microcosting determination carried out in 1999 (Chapter 7) were deflated using the Consumer Healthcare Price Index to produce adjusted bed day costs for each year of the study period [136]. The Consumer Healthcare Price Index was calculated for each year as the mean of the four commodity subgroup

indices, which relate specifically to the cost of healthcare i.e. medical fees, medicines and drugs, hospital charges and other medical expenses.

8.3.2 Cost of outpatient care

A gross costing approach was used to calculate total healthcare costs of providing outpatient care each year. The total cost each year was calculated as the sum of the constituent costs including:

- drug therapy costs
- laboratory investigations, blood products and investigative procedures
- other ambulatory costs including: (1) medical, nursing and paramedical costs, (2) medical, surgical and other consumables, (3) other pay and non-pay costs

Drug therapy costs

Drug costs were derived from Cliniscript® reports and calculated as the sum of expenditure on drugs dispensed in the satellite pharmacy to individual outpatients either subsequent to an outpatient consultation or on discharge following an inpatient episode. Expenditure on medication that was provided to the day ward was also included. Medication supplied to the day ward was estimated using a combination of dispensed reports from Cliniscript® specifying the day ward as a cost centre and individual patient's dispensed reports from Clinichemo® which details expenditure on chemotherapy dispensed according to location. Outpatient expenditure on home therapy of CMV retinitis, which had been calculated previously, as described in Chapter 6 was also included in the final calculation of total expenditure on outpatient pharmacotherapy. Drug therapy costs reflected purchase price to the hospital pharmacy department. Expenditure on antiretroviral therapy and on other medication used in the management of opportunistic infections and other complications of HIV disease was calculated for each year of the analysis.

Laboratory investigations, blood products and investigative procedures:

Annual resource consumption with regard to laboratory investigations and supply of blood products was requested from the relevant laboratory departments. Virology testing is provided by the National Viral Reference Laboratory, which as yet does not have the facility to provide an accurate estimation of individual resource consumption or unit costs. Therefore a number of assumptions based on the clinic's standard of care virology testing protocols were used to estimate the total resource consumption each year. These assumptions are listed in Appendix IV and take account of the size of the active cohort, the number of new attendees and the number of admissions for specific indications each year of the study. This data could be readily extracted from the recently constructed observational cohort database referred to in Chapter 2. Unit costs for virology were based on costs provided by laboratories outside the country. The total list of investigative procedures carried out on outpatients attending the day ward or clinic was abstracted from the hospital inpatient enquiry (HIPE) database. With the exception of virology tests, unit costs were provided by the relevant hospital departments and were consistent with prices charged to external customers. Annual expenditure on laboratory investigations, blood products and investigative procedures was derived from resource consumption and unit cost. Expenditure on laboratory investigations and blood products reflects population-pooled data, as individual expenditure was not available at time of analysis.

Other ambulatory costs

As mentioned in Chapter 7, there is a genitourinary medicine multidisciplinary team comprised of medical, nursing and paramedical staff dedicated to the provision of inpatient and outpatient care of individuals infected with HIV and other sexually transmitted diseases. Paramedical staff dedicated to this service exclusively includes clinical pharmacists, a clinical nutritionist and medical social workers. Members of this

multidisciplinary team were asked to assign a proportion to their time spent in the care of HIV and STD patients respectively. Time spent in the care of HIV-infected patients was further subdivided into time spent with either inpatients or outpatients. Using this weighting system the cost of staff time spent in the care of HIV-infected outpatients was calculated by multiplying the number or proportion of full time equivalents for each staff post employed each year by the relevant annual salary. Staff costs were derived from the midpoint on each respective salary scale. Staff costs included salary plus an additional 12% to account for administration and the employer's social insurance contribution, thereby reflecting the cost to the hospital.

Annual expenditure on medical, surgical and other consumables supplied to the genitourinary medicine outpatient department was requested from the hospital finance department. Following consultation with the clinic staff the proportion of total supplies attributable to the HIV outpatient and day ward attendance was assigned.

Other pay costs include catering, administration and other support staff (for example porters). Other non-pay costs include paramedical support, all hotel costs (cleaning, laundry, maintenance etc.), overheads and general administration. As described in the inpatient microcosting study, these costs were assigned on a square footage basis i.e. the same proportion of total hospital expenditure on these items per year as the proportion of entire square footage of the hospital occupied by the outpatient clinic and day ward. Following consultation with various managers in the outpatient department it was decided to apportion 1/3 of the annual cost for the clinic and day ward to the outpatient care of HIV-infected individuals. The remaining cost was attributed to the care of patients with other sexually transmitted diseases.

Actual expenditure on medical, surgical, other consumables and drug therapy in addition to pay scales for the multidisciplinary team were available for each year of the study. For all other areas of expenditure, costs available were 1999 costs and therefore were deflated using the Consumer Healthcare Price Index to produce adjusted prices for each year of the study [136]. The total cost of providing care to HIV-infected individuals each year was calculated as the sum of inpatient and outpatient expenditure. This figure was divided by the number of active patient years to give the mean annual cost of HIV care per active patient year. The mean annual expenditure on inpatient care, antiretroviral therapy, laboratory investigations, blood products and investigative procedures, and ambulatory care per active patient year was also calculated.

Outpatient contacts were defined as attendance at the outpatient clinic and day ward. The mean cost per outpatient contact was estimated by dividing the cost of providing outpatient care by the total number of contacts. As many of the constituent costs were only available for the day ward and the clinic in the aggregate, the mean costs per type of outpatient contact could not be estimated.

8.4 Results

Trends in expenditure on inpatient and outpatient care are summarised in Tables 8.1, 8.2, 8.3 and 8.4.

8.4.1 Cost of inpatient care

The annual cost of inpatient care decreased from IR£968,893 in 1995 to IR£821,555 in 1997 then increased somewhat to IR£883,950 in 1998 (Table 8.1). There was a further substantial increase in expenditure to IR£589,915 in the first 6 months of 1999 (IR£1,179,830 for 1999 ^{proj}). Expenditure on inpatient care per active patient in the cohort

Table 8.1 Total costs of inpatient care for HIV-infected individuals attending St James's Hospital each year from 1995 to 1999*.

	1995	1996	1997	1998	1999*	Cost per day (IR£)
Number of inpatient days:						
CD4 < 50 x 10^6/L	1,371	1630	962	1,134	605	IR£389
CD4 51-200 x 10^6/L	865	608	801	796	452	IR£358
CD4 > 200 x 10^6/L	433	322	534	513	615	IR£309
	1995 (IR£)	**1996 (IR£)**	**1997 (IR£)**	**1998 (IR£)**	**1999* (IR£)**	
Total cost of inpatient care according to baseline CD4 cell count	800,342	807,836	726,347	839,752	586,783	
Cost of inpatient stay per active patient year	2,493	2,141	1,728	1,826	2,292	

1999*: Data for first two quartiles of 1999 only

decreased each year for the first four years of the study from IR£3,018 in 1995 to IR£1,921 in 1998. Inpatient expenditure per active patient in the cohort actually increased in the last six months of the study period to IR£2,304.

8.4.2 Cost of outpatient care

Drug therapy costs

Outpatient expenditure on drug therapy increased more than four-fold from IR£457,112 in 1995 to IR£2,105,102 in 1998 and continued to increase in 1999 ^{proj} (Table 8.2). Annual outpatient drug expenditure per active patient in the cohort increased from IR£1,424 in 1995 to IR£4,576 in 1998 (Table 8.3). Total expenditure on antiretroviral therapy increased ten fold-from IR£175,951 in 1995 to IR£1,844,188 in 1998 and continued to increase in 1999^{proj}. Meanwhile expenditure on antiretroviral therapy per active patient in the cohort increased eight-fold over the study period. Overall drug costs were also analysed by therapeutic category for each year (Figure 8.1). The proportion accounted for by antiretroviral therapy increased from 38.5% in 1995 to 62.8% in 1996 and continued to increase in every subsequent year accounting for almost 90% of total drug expenditure in 1999*. The proportion attributed to other anti-infectives decreased over the study period from 34.2% in 1995 to only 5.4% in 1999*. The proportions attributed to each of the other therapeutic classifications including haematological agents, chemotherapy and other drugs also decreased over the study period.

Table 8.2: Total cost of outpatient care for HIV-infected individuals attending St James's Hospital each year from 1995 to 1999*.

	1995 (IR£)	1996 (IR£)	1997 (IR£)	1998 (IR£)	1999* (IR£)
Expenditure on medication	457,112	741,242	1,587,009	2,105,102	1,118,516
Expenditure on antiretoviral therapy	*175,951*	*465,486*	*1,327,872*	*1,844,188*	*1,018,729*
Laboratory investigations	144,710	277,275	362,264	383,408	207,995
Blood products	5,770	12,200	15,180	18,690	8,500
Investigative procedures	1,287	1,944	785	1,183	524
Specialist HIV multidisciplinary team	276,045	280,853	279,167	288,591	148,279
Other pay and non pay costs	46,392	47,992	49,592	53,325	28,262
Medical, surgical and other consumables	1,895	2,018	2,215	2,600	1,276
Total expenditure on outpatient care	**933,211**	**1,363,525**	**2,296,212**	**2,852,899**	**1,513,352**
Expenditure per outpatient contact	**354**	**495**	**770**	**835**	**758**

1999*: Data for first two quartiles of 1999 only

Table 8.3: Cost of outpatient care per active patient year for HIV-infected individuals attending St James's Hospital each year from 1995 to 1999*.

	1995 (IR£)	1996 (IR£)	1997 (IR£)	1998 (IR£)	1999* (IR£)
Expenditure on medication	1,424	1,965	3,776	4,576	4,369
Expenditure on antiretoviral therapy	*548*	*1,234*	*3,160*	*4,009*	*3,979*
Laboratory investigations	451	735	862	833	812
Blood products	18	32	36	41	33
Investigative procedures	4	5	2	3	2
Specialist HIV multidisciplinary team	860	744	644	627	579
Other pay and non pay costs	145	127	118	116	110
Medical, surgical and other consumables	6	5	5	6	5
Total Expenditure on outpatient care per active patient year	**2,907**	**3,614**	**5,464**	**6,202**	**5,912**

1999*: Data for first two quartiles of 1999 only

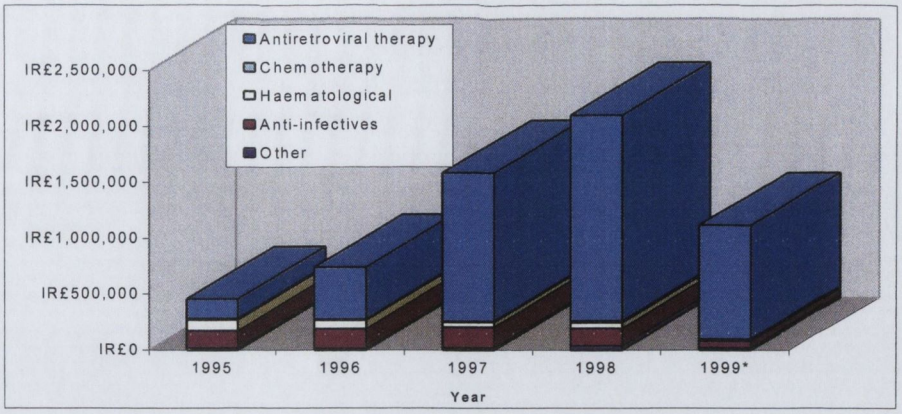


Figure 8.1 Outpatient expenditure on drug therapy according to therapeutic classification

Laboratory investigations, blood products and investigative procedures

An overall increase in total expenditure on laboratory investigations, blood products and investigative procedures was observed over the study period (Table 8.2). Laboratory investigations accounted for the majority of expenditure in this category. Expenditure per active patient year on laboratory investigations increased over the first 3 years of the study from IR£451 in 1995 to IR£862 in 1997 and then decreased in subsequent years to IR£833 in 1998 and IR£812 in 1999*(Table 8.3).

Other ambulatory costs

There was an overall 7% increase in the total cost of the specialist HIV multidisciplinary team comprising medical, nursing and paramedical staff from IR£276,045 in 1995 to IR£296,558 in 1999^{proj}(Table 8.2). The mean cost per active patient year decreased each year of the study from IR£860 in 1995 to IR£579 in 1999*(Table 8.3). There was an overall increase each year in the total cost of medical, surgical and other consumables but the mean cost per active patient year declined from IR£5.90 to IR£4.99 over the study period. Total expenditure on pay and non-pay costs increased slightly over the study

period. There was a decrease in expenditure on pay and non-pay costs per active patient year each year from IR£157 in 1995 to IR£106 in 1999*.

Cost per outpatient contact increased each year from IR£355 in 1995 to IR£757 in 1999* (Table 8.2).

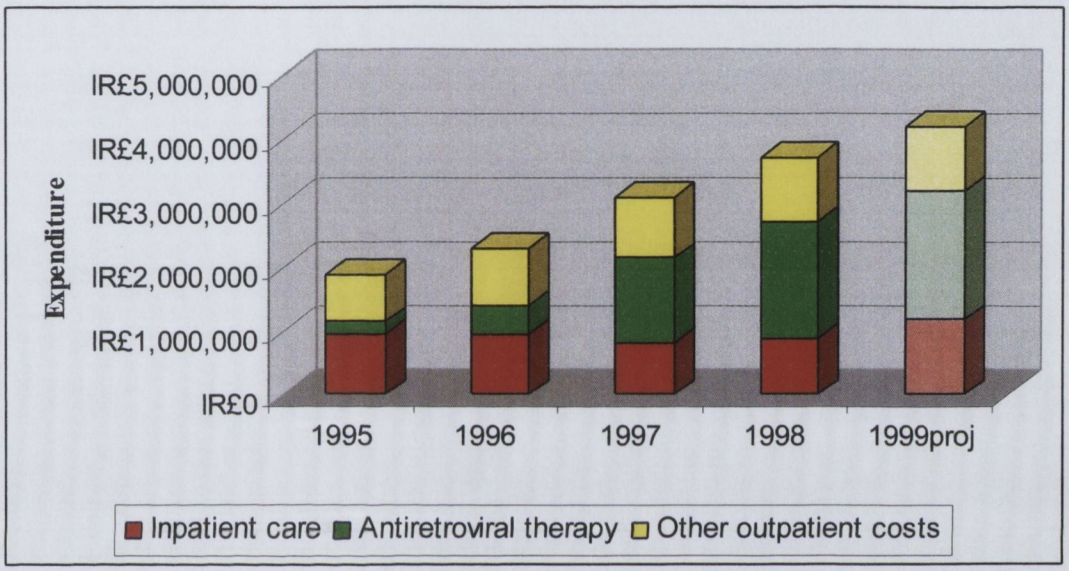


Figure 8.2 Total cost of providing HIV health care to patients attending St. James's Hospital from 1995 to 1999^{proj}.

From the hospital perspective, the annual cost of HIV care in our cohort increased from IR£1,906,191 in 1995 to IR£3,736,848 in 1998 increasing further to IR£2,102,107 in the first 6 months of 1999 (IR£4,204,214 for 1999^{proj}) (Figure 8.2) (Table 8.4). The greatest annual increase in expenditure was observed between 1996 and 1997. Inpatient costs, which accounted for approximately 50% of total expenditure on care of HIV-infected individuals in 1995, accounted for a decreasing proportion of total costs in each subsequent year up to 1998. In the last six months of the study, there was a slight increase in the proportion of total costs assigned to inpatient care from 23.6% in 1998 to 28.1% in 1999*. There was an overall increase in the proportion of total expenditure assigned to outpatient care over the study period. Total expenditure per active patient year increased from

Table 8.4 Total costs of HIV healthcare for patients attending St. James's Hospital each year from 1995 to 1999*

	1995 (IR£)	1996 (IR£)	1997 (IR£)	1998 (IR£)	1999* (IR£)
Total expenditure on inpatient care	**800,342**	**807,836**	**726,347**	**839,752**	**586,783**
Expenditure on drug therapy	457,112	741,242	1,587,009	2,105,102	1,118,516
Expenditure on laboratory tests, blood products and investigative procedures	151,767	291,419	378,229	403,281	217,019
Other ambulatory costs	324,332	330,863	330,974	344,515	177,818
Total expenditure on outpatient care	**933,211**	**1,363,525**	**2,296,212**	**2,852,899**	**1,513,352**
Total expenditure on HIV care	**1,733,553**	**2,171,361**	**3,022,559**	**3,692,651**	**2,100,135**
Total expenditure on HIV care per active patient year	**5,400**	**5,756**	**7,192**	**8,027**	**8,204**

1999*: Data for first two quartiles of 1999 only

IR£5,938 in 1995 to IR£8,211 in 1999* coincident with a decrease in mortality rate from 0.17 per active patient year in 1995 to 0.07 per active patient year in 1999*(Figure 8.3).

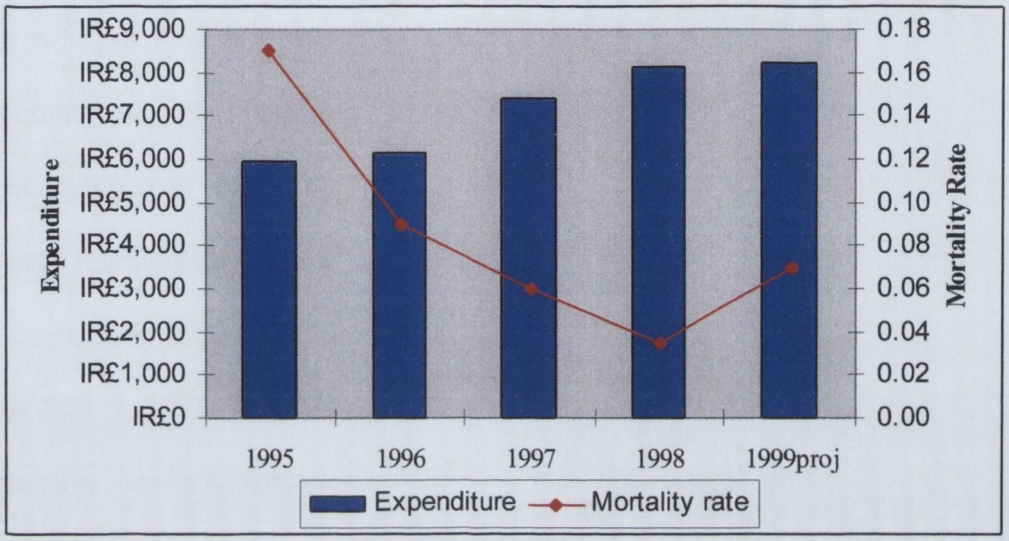


Figure 8.3 **Total cost of providing HIV health care and mortality rate per active patient year for 1995 to 1999*.**

8.5 Discussion

8.5.1 Cost of inpatient care

Inpatient per diem costs calculated in a microcosting study in 1999 (Chapter 7) and deflated using the Healthcare Consumer Price Index [136] were used to calculate total cost of hospitalisation for each year of the study by linking the number of inpatient days for patients in each CD4 cell count stratum with the relevant mean cost per inpatient day. The other factor, besides CD4 cell count at baseline shown to be a determinant of hospitalisation costs in Chapter 7, was the nature of discharge diagnoses for the particular period i.e. whether HIV-related or not. The proportion of all admissions attributable to HIV-related indications changed little over the study period accounting for between approximately 70% and 80% of all discharge diagnoses for each calendar year (Table 2.7).

Therefore it was considered reasonable to derive total hospitalisation costs from previously calculated CD4 cell count dependant costs.

Total expenditure on inpatient care decreased in the first three years of the study, increased somewhat in 1998 and then increased substantially in the first 6 months of 1999. Total expenditure is determined by the number of inpatient days and the proportion of inpatient days assigned to each CD4 cell count stratum. The cost per inpatient day exhibits an inverse relationship to CD4 cell count at admission (Table 7.7). An overall trend towards an increase in the proportion of inpatient days with CD4 cell count at admission greater than 200 x 10^6/L was observed over the study period (Table 8.1), resulting in less expensive inpatient costs per diem overall. A recent Spanish study also reported a decrease in the per diem costs of inpatient care in the post HAART era [137].

However, the overall number of inpatient days appears to be the most important determinant of cost of inpatient care. Despite variations each year in the proportion of inpatient days in each CD4 cell count stratum; the total cost of inpatient care mirrored the pattern of the number of inpatient days per year. The increase in mean length of stay in 1999 to 12.8 days from 9.5 days the previous year accounted for the substantial increase in the number of inpatient days in 1999 and therefore the increase in the total cost of inpatient care in that time period. Increased length of stay may be explained by examination of the discharge diagnoses for the first six months of 1999 as discussed in Section 2.5.6. As a consequence of the increase in the size of the active cohort each year, expenditure on inpatient care per active patient in the cohort decreased from 1995 to 1998. Despite a further increase in the number of active patients in the cohort in the first six months of 1999, expenditure per active patient actually increased because of the substantial increase in inpatient costs during that time period.

It is possible that this upturn in hospitalisation costs may indicate that the benefit of HAART in improving morbidity in the cohort is time limited. Follow-up studies are needed to investigate the durability of the benefits associated with HAART. Palella *et al* have shown a decline in the durability of successive HAART regimens [138]. The tendency to develop antiviral resistance may mean that the efficacy of this therapy in decreasing hospitalisation may wane over time unless drugs are developed that lack cross-resistance [139]. However in this case, such conclusions are premature as expenditure on inpatient care for 1999 may be subject to modification pending analysis of data for the latter half of the year.

8.5.2 Cost of outpatient care

Drug therapy costs

Unit drug therapy acquisition prices did not change over the study period as a consequence of a price freeze arrangement between the Irish Pharmaceutical Healthcare Association and the Department of Health and Children [140]. Outpatient expenditure on drug therapy increased by more than four fold over the study period as a consequence of increased cost per patient treated and an increase in the number of active patients in the cohort. The size of the active cohort increased from 321 active patient years in 1995 to 460 active patient years in 1998 (Table 2.1). The mean cost of drug therapy per active patient in the cohort increased three-fold from IR£1,424 in 1995 to IR£4,576 in 1998.

Outpatient drug therapy is comprised of antiretroviral therapy in addition to agents used in the management of opportunistic infection and other complications of HIV disease. Antiretroviral therapy accounted for 38.5% of total expenditure in 1995. By 1999* more than 90% of total expenditure was attributed to antiretroviral therapy. A similar trend of

increasing proportions of expenditure attributable to antiretroviral therapy was reported by Perdue *et al* who observed an increase from 34% in the pre-HAART era to 53% within 6 months of the first protease inhibitors becoming commercially available in the United States [141]. Outpatient expenditure on antiretroviral therapy increased ten fold between 1995 and 1998 coincident with the availability of new antiretroviral agents and a switch from dual therapy to HAART and as a result of expansion of the indications for antiretroviral therapy in 1996 (Section 1.1.2). This compares with a seven-fold increase in expenditure on antiretroviral agents after institution of HAART reported by a Washington group [139].

HAART which became available in the second quartile of 1996 is associated with a much greater drug acquisition cost than dual therapy, approximately IR£6-8000 and IR£2-3,000 respectively. Therefore, the greatest annual increase in expenditure on antiretroviral therapy occurred between 1996 and 1997 coincident with diffusion of HAART through the treated cohort (Figure 2.4). In addition, the unprecedented antiviral efficacy of these new antiretroviral strategies was associated with a substantial reduction in mortality (Figure 2.6). As a consequence of increased survival resulting in accrual of patients on antiretroviral therapy in addition to expansion of the treatment criteria, the proportion of the active cohort receiving antiretroviral therapy patients almost doubled from 31% in 1995 to 57% in 1998 further increasing the mean cost of antiretroviral therapy per active patient year (Table 8.3). Expenditure on antiretroviral therapy increased each year of the study period up to 1998. Although data for the first 6 months of 1999 only is available, expenditure seems to have plateaued at the 1998 level. Further increases in antiretroviral therapy expenditure per patient subsequent to the impact of the new treatment paradigms in 1996 may be attributed to an increased demand for salvage regimens containing 4 or more drugs. Salvage regimens which carry higher drug acquisition costs than the standard 3 drug

HAART regimens are required in patients who develop resistance to initial therapies. It is worth noting that a number of antiretroviral therapy agents, which were introduced during the study period, were initially available free of charge through expanded access programs. Agents available free of charge for up to 12-month periods prior to licensing included lamivudine, stavudine, saquinavir, abacavir and efavirenz. Therefore the observed increase in expenditure on antiretroviral therapy observed over the study period would have been greater still, had a cost been assigned to these agents.

In contrast to expenditure on antiretroviral therapy, mean expenditure per active patient on drug therapy other than antiretrovirals more than halved from IR£876 in 1995 to IR£390 in 1999*. Expenditure on other anti-infectives which was comprised mainly of treatment and prophylaxis of opportunistic infection accounted for a decreasing proportion of total drug expenditure each year of the study from 34.2% in 1995 to 5.4% in 1999*. This decline may be explained by the reduced incidence in AIDS defining illnesses from 46.1 per 100 active patient years in 1995 to 14.8 per 100 active patient years in 1999* (Table 2.5). In addition, the policy adopted in the clinic in 1997 of discontinuing primary and secondary prophylaxis of certain opportunistic infections in patients who respond immunologically and virologically to HAART has resulted in decreased expenditure on these regimens, which in the pre-HAART era were considered lifelong.

Haematological agents accounted for 21.4% of total drug expenditure in 1995. This category included agents used for treatment and prophylaxis of haematological dyscrasias associated with HIV infection and with the drugs used to treat HIV and other associated infections, which included filgrastim, immunoglobulin, erythopoetin etc. The proportion attributed to haematological agents almost halved between 1995 and 1996 and decreased markedly to account for a small proportion of total costs in every subsequent year (1.2% in

1999). The decrease in expenditure on haematological agents reflected an overall improvement in haematological morbidity due to a decreased incidence of HIV-induced bone marrow suppression, a decrease in the number of patients receiving myelosuppressive treatment for CMV retinitis (Table 5.2), a decreased proportion of patients receiving zidovudine with the availability of stavudine in 1996 and a reduced incidence of HIV dementia requiring high dose zidovudine (Table 2.5).

The small proportion of total expenditure attributed to other therapeutic classes including chemotherapy etc. accounted for a decreasing proportion of total expenditure over time. Despite a decrease in the annual cost of other medication, the overwhelming increase in the annual cost of antiretroviral therapy has resulted in a substantial increase in the mean cost of drug therapy per active patient over the study period. It is interesting to note that in 1995 the cost of other medication outweighed the cost of antiretroviral therapy. However since the introduction of HAART in 1996, expenditure on antiretroviral therapy accounted for an increasing majority of total drug expenditure for the remainder of the study period.

Laboratory investigations, blood products and investigative procedures

The overall increase in expenditure on laboratory investigations is a function of the increase each year in the size of the active cohort and the addition of lipid profiles and viral RNA measurement to routine testing protocols. The cost of laboratory investigations per active patient year increased for the first three years of the study and then declined for the remainder of the study period. In 1996, soon after the introduction of HAART, routine laboratory testing protocols were altered to include performance of lipid profiles on all patients prescribed protease inhibitors. Viral load testing became available in August 1996, thereby resulting in an additional substantial increase in expenditure on laboratory testing. Prior to the unprecedented antiviral success attained with HAART, patients receiving

antiretroviral therapy were routinely reviewed monthly or occasionally bimonthly. Because of the dramatic improvements in well being, the routine review period was extended to 3 months for patients stabilised on HAART regimens from 1997 onwards. The resultant decrease in the frequency of attendance for many patients therefore resulted in an overall decrease in the cost of laboratory investigations per active patient treated after 1997.

Other ambulatory costs

The cost of the HIV specialist team increased slightly over the study period. A small decrease in expenditure was observed in 1996 subsequent to a 50% reduction in dietician services. Improvement in the overall health status of the HIV-infected cohort in the era of HAART has resulted in a decreased requirement for dietetic services. However the substantial increase in the number of patients receiving antiretroviral therapy has resulted in an increased demand on pharmacy services and resulted in an increased allocation of pharmacy staff from the latter half of 1998 on. A research nurse and a research registrar were employed in the clinic from mid 1995 on. Although they contributed to the general services provided by the clinic in addition to their research activities, they were not included in this calculation because funding was derived from outside the healthcare system.

According to annual pharmacy reports available prior to this study, annual expenditure on medication dispensed from the outpatient pharmacy in the HIV clinic had increased from approximately IR£0.5 million in 1995 to IR£2 million in 1998. Subsequent to this analysis it emerged that expenditure on antiretroviral therapy had increased ten-fold from IR£175,951 in 1995 to IR£1,844,188 in 1998. The active cohort increased from 321 active patient years in 1995 to 460 in 1998 (Table 2.1). Therefore expenditure on antiretroviral therapy per active patient year increased eight-fold from IR£548 in 1995 to IR£4009 in

1998. Despite the initial increase in laboratory tests performed, other outpatient costs per active patient year decreased from IR£2,372 in 1995 to IR£2,193 in 1998. The decrease in the cost of inpatient care per active patient and the decrease in expenditure on other drug therapy offset the substantial increase in antiretroviral therapy costs. Despite the eight-fold increase in expenditure on antiretroviral therapy per active patient year over the study period and some lesser increases in other outpatient costs, the annual cost of HIV care per active patient increased by only a third from IR£5,938 in 1995 to IR£8,126 in 1998.

Prior to intensification of antiretroviral therapy strategies, drug therapy accounted for only 24% of total cost of care for HIV-infected individuals. Over the study an increasing proportion of total cost of care was attributed to drug therapy such that it accounted for the majority of total expenditure from 1997 on. Inpatient care accounted for a decreasing proportion of expenditure over the study period from 50.4% in 1995 to 23.6% in 1998. Torres and Barr reported an observed decrease in inpatient admissions and a coincident increase in outpatient contacts subsequent to adoption of HAART [66]. In our cohort, a decrease in admission rate and the number of inpatient days per active patient in the cohort has occurred without an increase in outpatient contact. Nevertheless, there is an apparent shift in expenditure from inpatient care to outpatient care, mainly as a consequence of increased expenditure on antiretroviral therapy.

Moore and Bartlett constructed a model of the cost-effectiveness ratio of HAART compared to previous standard HIV therapy with one nucleoside reverse transcriptase inhibitor [131]. They used observational data from their own cohort to estimate morbidity and mortality in the pre-HAART era and used estimates of HAART associated improvement in morbidity and mortality projected from the short term benefits of improvement in HIV RNA and CD4 cell count in slowing disease progression from a

recent study [25, 52]. Costs were derived from a multicentre US study [142]. This model yielded a cost-effectiveness ratio for HAART of $18,000 per year of life saved which compares favourably with the cost-effectiveness of other accepted therapeutic interventions in the US healthcare system including screening mammography ($30,000) and renal haemodialysis ($50,000). Sendi *et al* achieved comparable results using natural history and cost data from the Swiss HIV cohort study to model the cost-effectiveness of HAART compared to no antiretroviral therapy in their population. In the analysis limited to healthcare costs, the cost-effectiveness ratio of HAART ranged from $9,000 to $30,000 per life-year saved [143]. A number of centres have subsequently reported overall savings in the total cost of care per active patient [137, 144-147] whereas we have observed an incremental increase in expenditure per active patient of IR£2,273.

The extent to which the cost of intensification of antiretroviral strategies is offset by decreased expenditure on inpatient care and the management of opportunistic disease is dependant on the specific characteristics of the cohort and of the healthcare system in which the impact of the new strategies is evaluated. The cost of hospitalisation varies widely between countries. One study, which reported a decrease in overall HIV-related healthcare costs for a cohort managed by a Veteran Affairs hospital in Dallas, quoted an inpatient per diem cost of approximately $1,200, which is more than twice the cost of the most expensive bed day, used in our study [144]. Another American cost of illness study used Medicare reimbursement rates to estimate inpatient per diem cost at $1,606 [148]. As the majority of savings associated with HAART are derived from decreased hospitalisation costs, therefore these strategies will prove most cost-effective in centres with more expensive inpatient care.

The degree of immunosuppression of the cohort is also important. In our cohort, 88.4% of patients had CD4 cell counts < 500 x 10^6/L in 1995. The high degree of immunosuppression in our cohort has contributed to the cost-effectiveness of introducing HAART as standard of care. In a less immunosuppressed cohort, the incremental increase in the total cost of care would have been greater because the addition of HAART would have little impact on inpatient resource use and would result in an overall increase in resource utilisation. Indeed it has been suggested that overall savings in the total cost of providing care for a Californian Veterans Affairs HIV-infected cohort as a consequence of HAART compared to a slight increase in expenditure for a Denver Veterans Affairs cohort might be due to a greater degree of immunosuppression in the pre-HAART era amongst the Californian group, i.e. 81% and 55% respectively [146].

The real increase in the cost per patient over the 4 year period from 1995 to 1998 as a result of introducing HAART may be calculated as the sum of the difference between expenditure per patient in 1995 and expenditure per patient in each subsequent year. Therefore the real increase in annual expenditure per patient from 1995 to 1998 comes to IR£3,874. Mortality per patient treated declined from 0.17 in 1995 to 0.03 in 1998. The real cost per death avoided over the four-year period of the study was IR£27,671.

This chapter constitutes the first comprehensive description of the cost of providing specialist healthcare for HIV-infected patients in Ireland. Previously, attempts to evaluate the impact of any new intervention were hampered by the lack of contemporary baseline data on the use, cost and outcome of HIV service provision. Cost of illness evaluations such as this one provide a detailed account of resource consumption which facilitates comparison of the true cost impact of various therapeutic interventions for management of a disease and facilitates comparison with the cost impact of interventions used in other diseases to inform decision makers and allow prioritisation of resource allocation and

projection of future expenditure. Interpreting these results in the context of other cohorts requires an awareness of differences in access to care, healthcare costs and clinical status. However the results of this study may be considered applicable without modification for the Irish national cohort. Each of the 4 centres which provide specialist care to HIV-infected patients in Ireland are tertiary care teaching facilities and are grouped by the Department of Health and Children in the same cost of care category for purposes of reimbursement [39]. Therefore resource costs are considered to be applicable across the hospitals. Each centre adopted HAART as standard of care in 1996 and access to HAART is unrestricted within the Irish healthcare system. Comparing transmission risk, gender and clinical staging characteristics of our cohort with statistics reported for the national prevalent cohort reveals little variation. This finding is unsurprising considering that St. James's provides care to the majority of HIV-infected individuals who attend specialist centres. Hence the results from this study can be applied to the period prevalence of HIV infection in the country to project population costs of treating this disease.

From analysis of the results of this study, it appears that the cost of care of HIV-infected patients, which continuously increased in the first 4 years of the study, is now beginning to plateau. If results for the latter half of 1999 and 2000 provide further evidence to support this theory, then predictions for future expenditure on the care of HIV-infected individuals in the near future may be based principally on the size of the active cohort. In addition the template provided by this chapter may form the basis for the future evaluation of the impact of any new intervention adopted in the management of HIV disease. Because of the rapidly changing nature of HIV care, it is important that costing information is constantly updated and that real time data is used in estimating cost of care.

This study can contribute useful data on healthcare resource utilisation and costs in the management of HIV disease to projects such as the European Union Concerted Action program which aims to estimate epidemiological and socio-economic impacts of HIV

disease within the European Community [135]. To date, information from the countries which have the majority of patients with an AIDS diagnosis in the EC has been generalised to produce estimates of the healthcare burden of HIV disease for the EC as a whole. However access to care, uptake of HAART and mortality have been demonstrated to differ according to geographical location within the EC [50, 149]. One attempt to compensate for the lack of data for each country was to approximate data from neighbouring countries; for example UK resource consumption data was applied to Irish prevalence data. This strategy is compromised by the substantial differences in access to care and in particular access to antiretroviral therapy in recent years between the UK and Ireland.

In the UK, coincident with the availability of HAART and its attendant high drug acquisition costs, NHS funding for provision of care to HIV-infected individuals was actually cut from £200m in the financial year 1995/1996 to £186m in 1996/1997 [51]. Therefore, many regional health authorities were forced to restrict prescribing of HAART to individuals with CD4 cell counts $< 200 \times 10^6$/L. In contrast, no such restrictions were enforced in Ireland where criteria for initiation of antiretroviral therapy was expanded to include patients with CD4 cell counts $< 350\text{-}500 \times 10^6$/L and viral load >10,000 copies per ml coincident with the availability of expensive HAART regimens. Since the improvements demonstrated in morbidity, mortality and hospitalisation rate have been shown to be associated with HAART uptake, therefore the concept of applying UK resource consumption data which includes hospitalisation and antiretroviral therapy costs to Irish prevalence data may be no longer relevant.

8.6 Projecting expenditure on HIV specialist care

An informed prediction of the future cost of providing specialist care for the HIV-infected cohort at St James's Hospital was possible using the data generated in this thesis.

8.6.1 Construction of the model

A model was constructed to project expenditure for the years 2000 to 2002 inclusive using epidemiological data from Chapter 2 and cost of illness data from Chapter 8. This model was based on the following assumptions considered reasonable by the author:

- Data for the first six months of 1999 was assumed to be representative of the entire year.
- The number of incident patients each year was assumed to be the same as the figure for 1999 i.e. 116.
- The number of patients attending in $year_{n+1}$ = number of patients attending in $year_n$ – number of patients who died in $year_n$ + number of incident patients in $year_n$
- The ratio of the number of patients attending to the number of active patient years was assumed to be the mean of this ratio for each of the years 1995 to 1999 inclusive i.e. 1.2.
- The mortality rate was assumed to be the mean of the mortality rates for the post-HAART years i.e. 1997-1999 inclusive i.e. 5.3 deaths per 100 active patient years.
- The cost per active patient year was assumed to be the same as the cost in 1999 inflated using the healthcare consumer price index.
- The year on year increase in the healthcare consumer price index was assumed to be the same as the incremental increase for 1998/1999.

Using these assumptions, the number of patients attending, the number of active patient years, the number of deaths, the cost per active patient year and the total cost of providing HIV specialist care for the cohort was projected.

A sensitivity analysis was performed to investigate the impact of the following pessimistic and optimistic scenarios:

Pessimistic scenario
- increasing the incident number by 25%.
- decreasing the mortality rate by 25%.
- increasing the cost per active patient year by 25%.

Optimistic scenario
- decreasing the incident number by 25%
- increasing the mortality rate by 25%
- decreasing the cost per active patient year by 25%

8.6.2 Projected cohort size and expenditure

The projected size of the cohort and expenditure on HIV specialist care is documented in Table 8.5 and Figure 8.3. According to the model, the size of the active cohort will have increased to 742 active patient years by 2002 representing a 61.3% increase from 460 active patient years in 1998. Expenditure on HIV specialist care will have increased to IR£7 million in 2002 compared to IR£3.7 million in 1998 (89.2% increase). The pessimistic scenario would result in 164.9% increase in expenditure whereas in the optimistic scenario despite a 25% decrease in cost of care, enlargement of the active cohort would nevertheless produce a 24.3% in expenditure in 2002 compared to 1998.

The substantial increase in the size of the active cohort serves as an indication of increased pressure on clinic resources in the future and the need for expansion of the clinic infrastructure to cope with increased demand. The projected increase in expenditure represents a major demand on resources especially considering that Department of Health expenditure increased at a mean rate of 14% per annum over the years 1997 to 2000 [150]. Funding HIV specialist care to the current level would therefore require allocation of a greater proportion of overall resources in the future and diversion of resources from other areas. Using the cost and outcomes data collected in this thesis to determine the cost-effectiveness of HAART in the Irish healthcare system should help to inform decision makers charged with prioritisation of resources and it is hoped that this work will be completed in the future. However, such an approach is compromised by the lack of cost-effectiveness data in other therapeutic areas available for comparison to date.

8.6.3 Limitations of the model

Applying cost data to prevalence figures to project population expenditure for the national cohort is fraught with some difficulty. Uncertainty with regard to projected HIV incidence is complicated by escalating numbers of asylum seekers from areas of high prevalence, principally sub-Saharan Africa. Statistics for the year 2000 reveal a 37.5% increase in the number of asylum seekers [151], which therefore suggests that the increased incidence adopted in the pessimistic scenario may be more appropriate.

This model requires knowledge of the number of patients attending and the size of the active cohort. Whereas this information has been collated for the St James's cohort in this thesis, such statistics are unavailable for the other three centres in the country that provide adult specialist care. Expert opinion based on numbers receiving antiretroviral therapy at

each clinic suggests that the St James's population represents between 60 to 70% of the national cohort.

Projecting expenditure in HIV disease is difficult because of the dynamic nature of therapeutics in this area. In this thesis, the revolutionary impact of HAART on morbidity and mortality has been documented. Although a number of similar prevalence based projections of the burden of illness of HIV were conducted in the pre-HAART era[135, 152-154] no studies have been published in recent years. Since the database for this thesis closed, genotypic resistance testing has been adopted as standard of care to guide selection of antiretroviral therapy. Although this test is associated with a high acquisition cost, initial pharmacoeconomic evaluation in the French healthcare system has shown this intervention to be dominant largely due to cost savings on drug therapy[155].

Other interventions on the horizon which may impact on expenditure include phenotypic resistance and potentially therapeutic drug monitoring of antiretrovirals. In addition, a new class of antiretroviral agents called the fusion inhibitors, which it is anticipated will be administered in combination with standard HAART regimens, will shortly be available [156]. The evolution of substantial HIV resistance to antiretrovirals which has been documented recently in patient populations [157, 158] and subsequent increased requirement for salvage regimens containing greater numbers of drugs may also impact negatively on drug expenditure. However, because of considerable toxicity associated with HAART therapy, the most recent antiretroviral guidelines recommend a more conservative approach to initiation of HAART [159], and may therefore result in savings on drug acquisition cost. It is apparent that therapeutics in HIV disease is continuing to evolve rapidly and cost projections will need to be adjusted on an ongoing basis following assessment of the impact of new strategies.

Some population based projections of expenditure in the pre-HAART era employed sophisticated methodologies including empirical Bayesian estimators for reconstruction of HIV incidence and prevalence and scenario based epidemiological modelling [135, 160]. Such techniques should produce more accurate estimations of expenditure. Nevertheless, the simple model used here to predict burden of illness indicates that management of HIV disease will represent an increasing drain on healthcare resources in the next few years.

Table 8.5 **Projected prevalence, incidence, deaths, cost per active patient year and total expenditure for the HIV-infected cohort attending St James's from 1999 to 2002.**

	1999	2000	2001	2002
Number of patients attending	638	726	810	890
Number of active patient years	532	605	675	742
Number of incident patients	116	116	116	116
Number of deaths	28	32	36	39
Expenditure per patient year	IR£8,204	IR£8,614	IR£9,024	IR£9,435
Total expenditure on HIV care	**IR£4,361,793**	**IR£5,210,311**	**IR£6,089,699**	**IR£6,997,328**

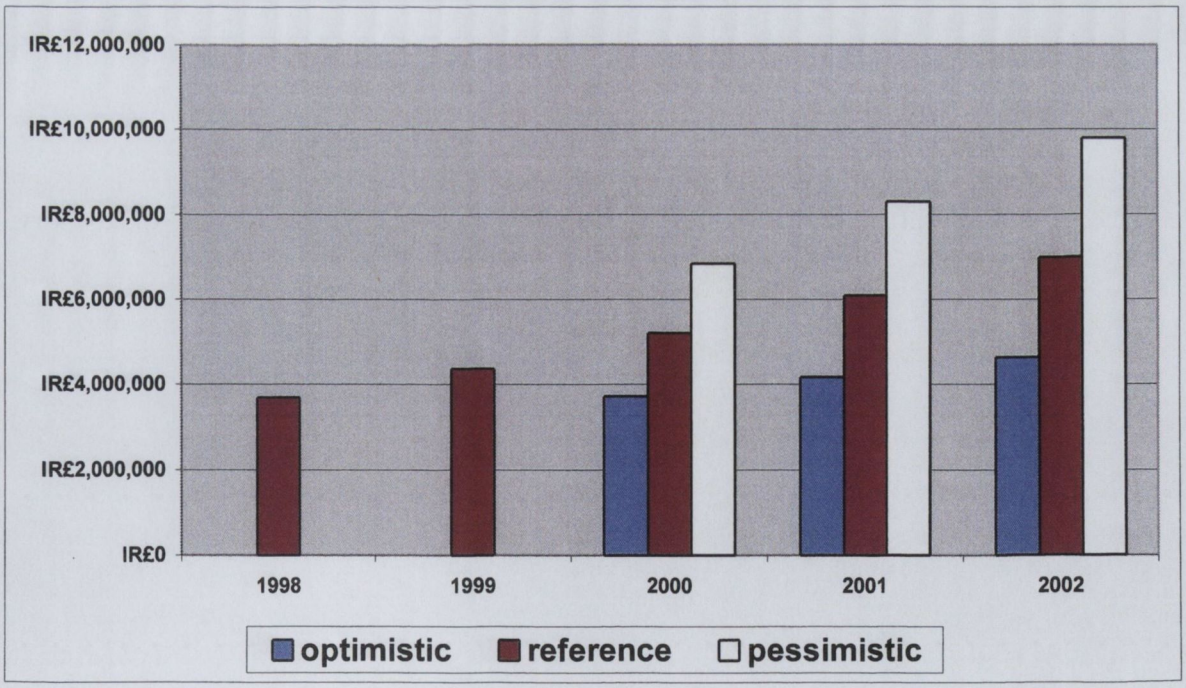


Figure 8.4 **Measured expenditure on specialist HIV care for 1998 and projected expenditure for the years 1999 to 2002 inclusive based on reference, optimistic and pessimistic scenarios.**

8.7 Conclusion

The absolute cost of providing HIV healthcare doubled from approximately 2 million to 4 million coincident with adoption of HAART as standard of care and expansion of the criteria for initiation of antiretroviral therapy (Figure 8.2). However during this time period dramatic improvements in surrogate markers of disease progression and clinical endpoints of morbidity and mortality were noted (Chapter 2). Decreased utilisation of inpatient services has occurred without a coincident increase in demand for outpatient services per active patient in the cohort. However, the coincident increase in the size of the cohort has resulted in an increase in the absolute number of outpatient contacts and a reversal of the initial decrease in the absolute number of inpatient days. The resultant increase in workload has implications for planning future service provision.

The cost of antiretroviral therapy per active patient year increased from IR£548 in 1995 to IR£3,979 in 1999*. The decrease in the cost of inpatient care per active patient and the decrease in expenditure on other drug therapy offset the substantial increase in antiretroviral therapy costs. Despite the eight-fold increase in expenditure on antiretroviral therapy per active patient year over the study period and some lesser increases in other outpatient costs, the annual cost of HIV care per active patient increased by only a third from IR£5,938 in 1995 to IR£8,211 in 1999*.

This chapter provides important descriptive data, which is essential for future pharmacoeconomic evaluations in HIV healthcare. As demonstrated by this chapter, adoption of HAART is associated with substantial financial outlay. Use of HAART is also complicated by non-monetary costs such as iatrogenic morbidity associated with constituent drugs including the protease inhibitors. In the next chapters, the tolerability profiles of the protease inhibitors will be examined.

CHAPTER 9

9 CONSTRUCTION OF COMPARATIVE TOLERABILITY PROFILES FOR THE PROTEASE INHIBITORS

9.1 Introduction

Factors which influence selection of a specific protease inhibitor include the patient's clinical status, the resistance profile of the virus based on previous antiretroviral exposure or the results of phenotypic and/or genotypic resistance assays, the fit of the drug administration schedule to the patient's lifestyle, and the drug's tolerability profile. The construction of comparative tolerability profiles for the protease inhibitors would contribute to risk benefit analysis, aid drug selection and facilitate individualisation of drug therapy to the patient.

Tolerability profile is considered to be an important determinant of adherence to antiretroviral therapy [161]. The consequences of non-adherence include lack of viral suppression, subsequent emergence of resistant mutations and ultimately loss of anti-viral efficacy. Therefore in the interest of optimising the risk-benefit ratio and maximising the cost-effectiveness of antiretroviral therapy, a clear understanding of the issues contributing to drug adherence including the incidence, severity, presentation and management of adverse drug reactions is required.

Drug toxicity has long been an important issue in the management of HIV-infected individuals. Adverse reactions to drugs are extremely common in HIV infection, especially amongst those in the most advanced stage of disease. Factors, which may account for the high incidence rate of adverse drug reactions (ADRs) amongst HIV-infected individuals, include [162]:

- the intrinsic toxicity of many of the agents used
- the duration of exposure to many drugs: antiretroviral agents are usually required for the remainder of the patient's life and drugs used in the prophylaxis and management of opportunistic illnesses are frequently prescribed for long periods of time
- an increased scope for drug interaction which may enhance toxicity due to the multiplicity of agents prescribed to HIV-infected patients
- altered drug metabolism either as a consequence of HIV infection or common co-morbidities, for example hepatitis B and C

An adverse drug reaction has been defined as any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use [163]. Adverse drug reactions have been categorised according to an alphabetic classification as summarised in Table 9.1 [164]. Due to the limited number of patients exposed to any agent prior to licensing, post marketing surveillance frequently reveals category B and C ADRs which were hitherto unknown. Ongoing monitoring of the literature to ensure an up to date knowledge of tolerability profiles is of paramount importance for newly licensed therapies. The protease inhibitors first became available in Ireland in 1996. The initial studies indicated the protease inhibitors to be relatively well tolerated. Since the tolerability profiles of each of the five protease inhibitors available for use in Ireland differ to some degree, it was considered useful to collate all currently available information detailing adverse drug reactions to these agents.

Table 9.1: Alphabetic classification of types of adverse drug effects [164].

Type	Type of effect	Definition
A	Augmented pharmacological effects	Adverse effects that are known to occur from the pharmacology of the drug and are usually dose related and therefore readily reversible on dose reduction or withdrawal. They are seldom fatal and relatively common.
B	Bizarre effects	Adverse effects that occur unpredictably are not dose related, and often have a high rate of morbidity and mortality. These are uncommon.
C	Chronic effects	Adverse effects that only occur during prolonged treatment and not with single doses

9.2 Aim

The aim of this chapter was to conduct an extensive literature search to identify and estimate the incidence of adverse drug reactions associated with each of the protease inhibitors. This would facilitate construction of a tolerability profile for each drug and ultimately the production of a guide to the tolerability profiles of these agents in an easy to use format for health care professionals. Furthermore these profiles could from the basis

for comparison of the incidences of adverse drug reactions to specific agents observed in our clinical cohort with rates previously reported in the literature.

9.3 Method

A systematic literature search was undertaken to facilitate collation of all available information detailing tolerability of the protease inhibitors. Standard reference sources used included the manufacturers' Summaries of Product Characteristics (Ireland, UK and US) and standardised pharmacopoeias including the American Hospital Formulary System® and Micromedex®. In addition data was abstracted from publications identified by a Medline® and Iowa Drug Information System® search using the key words adverse drug reaction/tolerability/side effect combined with each protease inhibitor. Conference proceedings from international meetings in the last five years were also searched for relevant additional information. Data collection was censored on the first of February 2000

A database was constructed in which each protease inhibitor was assigned an occurrence and an incidence rating for a range of adverse drug reactions. For each adverse drug reaction identified in the literature, the following information was entered in the database:

- the nature of the adverse drug reaction,
- the protease inhibitor implicated,
- the reported incidence of the adverse drug reaction,
- an indication of the causal relationship between the protease inhibitor and the adverse drug reaction.

The incidence rate at which each adverse drug reaction occurred for specific protease inhibitors was then classified according to the following scale: <2%, 2 - <10%, 10 - <20%, ≥20%. In the instance of case reports of an adverse drug reaction, where the incidence was unknown and the causal relationship between the protease inhibitor and this event may not have been established, the incidence rate was highlighted, for example <2*%. In cases

where incidence data for monotherapy and combination therapy were available, the results of the monotherapy study were used as a more accurate reflection of the incidence at which an adverse drug reaction could be attributed to the specific protease inhibitor alone. In addition, some adverse drug reactions had not been recognised in the pre-marketing era. The incidence of these newly recognised side effects was abstracted from clinic based toxicity surveillance studies.

The resulting database included the incidence rate of more than 300 adverse drug reactions for each of the five protease inhibitors. An abridged version including approximately 150 side effects was produced. Priority was given to side effects which were either frequently observed, considered serious or were deemed clinically important by a review panel including the author, senior physicians and senior clinical pharmacists from the Department of Genito-Urinary Medicine, St James's Hospital, Dublin and the Division of Infectious Diseases, North Western Memorial Hospital, Chicago. The tolerability profile of the protease inhibitors was depicted with easily interpretable symbols representing each incidence rate range as follows:

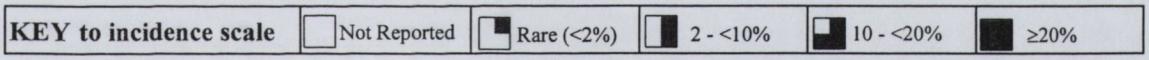


Table 9.2 Comparative tolerability profiles of the protease inhibitors.

ADVERSE REACTION	AMP	IDV	NLF	RTV	SQV
ALLERGIC					
Allergic reaction	☐	☐	◔	◔	◔
Anaphylaxis	☐	◔	☐	◔*	☐
Angioedema	☐	☐	☐	◔	☐
Atopic rhinitis	☐	☐	☐	☐	◔
Bronchospasm	☐	☐	◔*	◔*	☐
Facial oedema	☐	☐	◔*	◔	☐
Stevens-Johnson syndrome	◔	◔*	☐	◔*	◔*
Urticaria	☐	◔*	◔	◔	◔
CARDIOVASCULAR					
Hypotension	☐	☐	☐	◔	◔
Syncope	☐	☐	☐	◔	◔
Vasodilation	☐	☐	☐	◔	◔
CENTRAL NERVOUS SYSTEM					
Anxiety	☐	☐	◔	◔	◑
Asthenia/fatigue	◔	◑	◔	◑	◑
Ataxia	☐	☐	☐	☐	◔*
Confusion	☐	☐	☐	◔	◔
Depressed mood	◑	☐	◔	◔	◑
Headache	◕	◑	◔	◑	◑
Hyperaesthesia	☐	◑	☐	◔	◔
Insomnia	☐	◑	◔	◑	◑
Paraesthesia-circumoral	●	☐	☐	◑	☐
Paraesthesia-peripheral	◑	◑	◔	◑	◔
Seizure	☐	☐	◔	◔	◔
Somnolence	☐	◔	◔	◑	◔
Suicidal ideation	☐	☐	◔	☐	◔*

KEY to incidence scale	☐ Not Reported	◔ Rare (<2%)	◑ 2 - <10%	◕ 10 - <20%	● ≥20%

Table 9.2 (Contd.) Comparative tolerability profiles of the protease inhibitors.

ADVERSE REACTION	AMP	IDV	NLF	RTV	SQV
ENDOCRINE/METABOLIC CONTD.					
Hypoglycaemia	☐	☐	◔	☐	◔
Hypothyroidism	☐	☐	☐	*◔	◔
Lactate dehydrogenase ⇑	☐	☐	◔	◔	☐
EAR, NOSE AND THROAT					
Cerumen ⇑	☐	☐	☐	◔	☐
Ear ache	☐	☐	☐	◔	◔
Ear pressure	☐	☐	☐	☐	◔
Epistaxis	☐	☐	☐	◔	◔
Hearing impairment	☐	☐	☐	◔	◔
Pharyngitis	☐	◔	◔	◑	◔
Rhinitis	☐	☐	◔	◔	☐
Sinusitis	☐	◔	◔	☐	◔
Throat irritation	☐	☐	☐	◑	☐
Tinnitus	☐	☐	☐	◔	◔
GENITOURINARY/RENAL					
Haematuria	☐	◔	☐	◔	☐
Hydronephrosis	☐	◔	☐	☐	☐
Impotence	☐	☐	◔	◔	◔
Nephrolithiasis	☐	◑	◔	◔	*◔
Proteinuria	☐	◔	◔	☐	☐
Renal insufficiency	☐	*◔	☐	*◔	*◔
GASTROINTESTINAL					
Abdominal distention	☐	*◔	*◔	◔	◔
Abdominal pain	*◔	◑	◑	◑	◑
Acid regurgitation	☐	◔	☐	☐	☐
Amylase ⇑	☐	◑	◔	◔	◔
Anorexia	☐	◔	◔	◔	◔
Chelitis	☐	☐	☐	◔	◔
Constipation	☐	☐	☐	☐	◔

KEY to incidence scale	☐ Not Reported	◔ Rare (<2%)	◑ 2 - <10%	◕ 10 - <20%	■ ≥20%

9.4 Discussion

Ritonavir, saquinavir and indinavir were approved by the FDA in 1996 and were available for use on an unlicensed basis in Ireland later that year. Nelfinavir was introduced in 1997, and therefore a considerable amount of information exists in the literature detailing the toxicity of these four agents. Amprenavir has only been available in this country since mid 1999 and is as yet unlicensed. Therefore, there is a relative paucity of information published other than the pre-marketing studies. Many of the adverse drug reactions that have been attributed to the protease inhibitors may be considered a class effect, for example gastrointestinal and hepatic effects. Others appear to be drug specific or at least to occur at an increased frequency in association with a particular drug, for example perioral paraesthesia with ritonavir and amprenavir or nephrolithiasis with indinavir. Not all of the adverse drug reactions now attributed to the protease inhibitors were identified prior to approval by the licensing bodies. A number of idiosyncratic Type B adverse drug reactions have been identified subsequently. On occasion, discrepancies arose in the incidence rate reported for specific adverse drug reactions. This usually occurred when an adverse drug reaction identified during pre-marketing trials was subsequently noted to occur at a greater frequency, either following extensive use in clinical practice or during post-marketing surveillance studies by the manufacturers.

9.4.1 Gastrointestinal effects

Gastrointestinal adverse effects include diarrhoea, which occurs at a frequency of over 20% with amprenavir and nelfinavir and at an incidence of 10-20% with ritonavir and saquinavir [90, 165-167]. This iatrogenic diarrhoea is often transient in nature occurring during the first month of therapy and usually responds well to anti-motility agents, for example loperamide. Occasionally if required, patients are maintained indefinitely on loperamide as adjunctive therapy. Abdominal discomfort has been reported in 2-10% of

patients receiving indinavir, ritonavir, nelfinavir and saquinavir and in <2% of patients prescribed amprenavir, whereas flatulence has been reported in 2-10% of patients on indinavir, nelfinavir and saquinavir and in <2% of those on amprenavir and ritonavir [90, 165-168]. Nausea and vomiting which occur with each of the protease inhibitors, are most frequently associated with ritonavir and amprenavir (nausea in >20% and vomiting in 10-20% of patients) and least likely with nelfinavir (nausea in 2-10% and vomiting in <2% of patients)[90, 165, 166]. Dyspepsia is most commonly associated with indinavir (10-20%) but has also been reported with saquinavir (2-10%) and nelfinavir (<2%) [166, 168-170]. Dietary restrictions, which aim to optimise the bioavailability of indinavir, stipulate that the drug must be taken at least 30 minutes before food and 2 hours after food. Taking indinavir in the fasting state may contribute to the dyspepsia associated with this agent. All of the other protease inhibitors may be taken with food. Taste perversion has been reported in 10-20% of patients receiving ritonavir, 2-10% of patients receiving amprenavir, indinavir and saquinavir but has not been reported in association with nelfinavir [90, 165, 168-170].

9.4.2 Hepatic effects

Protease inhibitors undergo extensive metabolism via the mixed function oxidase enzyme complex, cytochrome P450. Many HIV-infected patients are co-infected with hepatitis B and/or C. Therefore, hepatic abnormalities in association with the use of protease inhibitor therapies in HIV-infected individuals are not unexpected. There have been rare reports of clinical hepatitis in association with all of the licensed protease inhibitors [171-173]. Raised amino transferase levels have been reported in 2-10% of patients prescribed ritonavir, saquinavir and indinavir and in <2% of patients prescribed nelfinavir [90, 166, 168-170]. Increases in gamma glutamyl transferase and alkaline phosphatase have been noted in association with ritonavir, saquinavir and nelfinavir use [90, 166, 169, 170]. Indirect hyperbilirubinaemia has been documented in approximately 10% of patients

taking indinavir and is accompanied by increases in aminotransferases in less than 1% of patients [168]. Indirect hyperbilirubinaemia appears to be a drug specific effect with no proven clinical sequelae.

9.4.3 Dermatological effects

The dermatological adverse effects noted with the protease inhibitors include rash, dry skin, alopecia, paronychia and ingrown toenails. Rash has been reported most commonly with amprenavir and indinavir, occurring at an incidence of 10-20% [165, 168]. There have been case reports of alopecia with indinavir and saquinavir [167, 174, 175]. Ritonavir and saquinavir have been associated with photosensitivity [90, 169]. Bouscarat *et al* reported paronychia and ingrown nails on the great toes of 42 patients prescribed indinavir i.e. 4% of all patients prescribed indinavir, during a 1 year follow-up [176]. There have also been case reports of paronychia in patients exposed to ritonavir and saquinavir [177].

9.4.4 Nephrolithiasis

Nephrolithiasis identified as a drug specific side effect of indinavir during pre-marketing studies was originally estimated to have an overall incidence of approximately 4% [168]. Subsequently, pooled data from several clinical trials indicated that nephrolithiasis accompanied by flank pain occurred in approximately 9% of patients prescribed indinavir and resulted in discontinuation of the drug in 4% of these patients [168]. The clinical syndrome may include back or loin pain, haematuria and proteinuria. Occasionally nephrolithiasis is accompanied by renal insufficiency [178-180]. In one study, Kopp *et al* reported the presence of indinavir urinary crystals in 29 of 142 patients prescribed indinavir (20%) [181]. Kopp postulated that indinavir is associated with a continuum of crystal related syndromes ranging from asymptomatic crystalluria to frank nephrolithiasis.

Indinavir is poorly soluble at a pH above 6.0 (< 0.03mg/ml) [182]. Although indinavir is excreted principally in the faeces, 19% is recovered in urine both as unchanged drug and metabolites. Limited solubility of the drug in its free base form may lead to precipitation of crystals in the renal collecting system, leading to obstruction and the associated symptoms of renal colic. Dehydration and consequent concentration of the urine may predispose to crystal formation. Patients prescribed indinavir are advised to minimise the risk of nephrolithiasis by maintaining a fluid intake of at least 1.5 litres daily [168]. Patients are advised to further increase their fluid intake if exercising or during periods of warm weather, since the incidence of nephrolithiasis has been shown to correlate with environmental temperature [183]. Patients should also increase their intake of water when consuming alcohol to overcome the resultant dehydration.

Isolated incidences of nephrolithiasis in patients prescribed ritonavir, nelfinavir and saquinavir have been reported, however the causal relationship has not been established [184-188].

9.4.5 Increased tendency to bleed amongst haemophiliacs

Subsequent to licensing of these agents, an increased risk of bleeding, spontaneous haematomas and haemarthroses has been reported in haemophiliac patients receiving protease inhibitors [189, 190]. Yee *et al* reported unusual episodes of bleeding in three patients with haemophilia A soon after the initiation of protease inhibitors [191]. In this study, all patients discontinued therapy because of increased bleeding. In another study of seventeen HIV-infected patients receiving protease inhibitor therapy, ten patients reported increased bleeding or changes in bleeding pattern in the first six months of therapy. Eight patients reported increased demand for blood products over this time period [189]. In most cases protease inhibitors were continued or reintroduced.

9.4.6 Hyperlipidaemia

The first protease inhibitor to be associated with hyperlipidaemia was ritonavir. In the initial phase III studies, statistically significantly more patients in the ritonavir treated groups had elevated triglycerides as compared with the placebo group. Two of the earliest published double blind placebo controlled studies documented hypertriglyceridaemia and hypercholesterolaemia associated with ritonavir [43, 44]. Markowitz *et al* reported doubling of baseline triglyceride and cholesterol values in 61% and 8% of patients on ritonavir respectively compared with 19% and 0% of patients taking placebo [44]. Post-marketing surveillance has identified case reports of hyperlipidaemia associated with indinavir and the product information for nelfinavir lists hyperlipidaemia at an incidence <2% [166, 192]. The American Summary of Product Characteristics for amprenavir reports elevated triglycerides in 10-20% of patients and elevated cholesterol in < 2% of patients in phase III studies [165].

In contrast to company data, results from a number of observational clinical studies suggest greater incidences of dyslipidaemia associated with protease inhibitors. A large retrospective review of 453 patients receiving protease inhibitors reported a 14% prevalence of hypercholesterolaemia [193]. A number of observational cohort surveillance studies report the incidence of hypercholesterolaemia at 40-44% for ritonavir, 7-35% for indinavir, and 14-40% for nelfinavir with the incidence of hypertriglceridaemia at 80% for ritonavir, 51% for indinavir and 49% for nelfinavir [194-196] A study of 38 patients on soft-gel saquinavir reported incidences of elevated triglycerides and cholesterol between 2-10% [197]. However in many of these studies it is unclear whether fasting or non-fasting samples were used. In one study non-fasting samples at initiation of protease inhibitor therapy were compared to fasting samples during the study period, which may underestimate the elevations in lipid levels particularly with respect to triglycerides [196].

In summary, hyperlipidaemia including elevations of both triglycerides and cholesterol is a common feature of treatment with each of the HIV-1 protease inhibitors currently available. Elevation of triglycerides does appear to occur more frequently than elevation in serum cholesterol and to occur most commonly with ritonavir containing regimens. Hyperlipidaemia in other patient populations has been associated with long term sequelae including pancreatitis and atherosclerosis. Therefore the metabolic consequences of treatment with potent protease inhibitors has become increasingly relevant particularly in view of increased survival associated with these agents [12].

9.4.7 Pancreatitis

Increased amylase and pancreatitis have been reported to occur at an incidence < 2% with nelfinavir, ritonavir and saquinavir [167, 186, 198]. Although hyperamylasaemia has been reported in 2-10% of patients on indinavir, no cases of resultant pancreatitis have been documented to date [192]. It is often difficult to determine causality of pancreatitis in HIV-infected patients who may be co-prescribed other agents such as didanosine, pentamadine, stavudine etc., which may also predispose them to this presentation. However, in view of the high incidence of hypertriglyceridaemia (which is an independent risk factor for pancreatitis) associated with protease inhibitors, it is possible to assume that elevated triglycerides may have contributed in part to the development of pancreatitis in patients prescribed these agents.

9.4.8 Vascular complications

There have been a number of reports of premature vascular complications, for example myocardial infarctions linked to the use of protease inhibitors [199-204]. A retrospective study of more than 1300 patients suggested an increased frequency of myocardial infarction in patients prescribed protease inhibitors [205]. However two other retrospective studies of almost 3000 and 4000 patients respectively showed no such association [206,

207]. Hyperlipidaemia is a well-known risk factor for atherosclerosis and premature coronary artery disease. HIV-infected patients may be at risk from premature cardiac events independently of protease inhibitor induced hyperlipidaemia. [208]. Therefore for a given lipid profile, an HIV-infected person may be at increased risk of atherosclerotic disease above what may be suggested by general population studies [209].

Although the association between protease inhibitor induced hyperlipidaemia and long term vascular sequelae is unclear, there is however sufficient evidence to suggest cause for concern. In many centres, patients who demonstrate hyperlipidaemia subsequent to antiretroviral therapy are being managed according to established guidelines to minimise the risk of vascular complications, which include lifestyle modification and possible initiation of lipid lowering therapy depending on laboratory values and assessment of other risk factors for atherosclerotic disease. Lipid lowering therapy however should only be initiated after due consideration of secondary causes, for example diabetes mellitus, hypothyroidism, potential drug interactions and overlapping toxicity. Recent guidelines advocate these strategies [74]. Long term prospective studies are needed to investigate the relationship between protease inhibitors and vascular complications and to determine optimal management strategies.

9.4.9 Diabetes

In June 1997, the FDA issued a warning to physicians of the possibility that use of protease inhibitors may lead to hyperglycaemia, new onset diabetes mellitus or exacerbation of pre-existing diabetes mellitus. As of 12th May 1997, a total of 83 cases of diabetes mellitus or hyperglycaemia and 5 cases of diabetic ketoacidosis had been reported to the FDA. [210]. Impaired glucose tolerance and hyperglycaemia have been reported with each of the currently available protease inhibitors [211-213]. Caldwell *et al* reported protease inhibitor associated hyperglycaemia in 11.5% of 216 HIV-infected patients [214]. The prevalence of

hyperglycaemia was 11.6%, 4.3%, and 8.2% in patients prescribed indinavir, saquinavir and nelfinavir respectively. In a retrospective 1 year review of 783 HIV-infected patients, Mauss *et al* found treatment with protease inhibitors to be statistically significantly associated with hyperglycaemia, ($p<0.005$) [215]. Hyperglycaemia was documented in 16% of patients receiving indinavir, 9% receiving saquinavir, 9% receiving nelfinavir and <2% receiving ritonavir. According to the manufacturer's Summary of Product Characteristics for amprenavir the reported incidence of hyperglycaemia was 2-10% [165]. Other studies report an overall incidence of hyperglycaemia in 3-5% of patients prescribed protease inhibitors [216-218]. Patients on protease inhibitors should have their blood glucose measured periodically and should be warned to report symptoms of hyperglycaemia such as polyuria, polydypsia etc. [219].

9.4.10 Fat redistribution syndrome

A syndrome of abnormal fat redistribution has been reported in patients on protease inhibitors although a causal relationship with these agents has not been established [220-225]. This syndrome may include some or all of the following features: peripheral lipodystrophy or fat wasting, central adiposity (truncal obesity), dorsocervical fat enlargement, breast enlargement and gynecomastia. In addition to the above features of fat redistribution, some patients demonstrate elevated triglycerides and elevated cholesterol together with insulin resistance, which indicates an underlying metabolic abnormality. Carr *et al* proposed that the binding of protease inhibitors to two proteins that regulate lipid metabolism, cytoplasmic retinoic-acid-binding protein type 1,and low-density lipoprotein receptor protein, is responsible for abnormal lipoprotein metabolism, insulin resistance and the morphologic changes seen in this syndrome [226].

Besides fat redistribution syndrome, other unusual adverse drug reactions reported with protease inhibitors include dry skin, dry lips, alopecia and nail dystrophy for which a

disturbance in retinoic acid metabolism is again a possible explanation. Since lipoprotein receptor protein is also responsible for clearance of tissue plasminogen activator, the increased bleeding tendency which has been reported in haemophiliacs receiving protease inhibitors may potentially be explained by inhibition of uptake of endogenous tissue plasminogen activator [226].

Estimates of the prevalence of a fat redistribution syndrome are hampered by the lack of accepted diagnostic criteria. However, Carr *et al* have suggested a classification including clinical anomalies of fat redistribution (lipodystrophy) and metabolic abnormalities. Using this classification, a number of studies suggest that the incidence of fat redistribution ranges from 40-74% amongst patients treated with protease inhibitors regardless of the protease inhibitor prescribed [227-229]. It has been suggested that duration of exposure to protease inhibitors greatly increases the risk of this effect [225].

Fat redistribution accompanied by hyperlipidaemia was initially reported in association with the protease inhibitors. However more recently, similar clinical presentations have been reported with the other constituents of HAART i.e. reverse transcriptase inhibitors [230-234]. Therefore it has been hypothesised that this syndrome may result from prolonged suppression of HIV infection in patients with advanced disease and that the protease inhibitors may be a co-factor for precipitation of this syndrome rather than the direct cause of it. The pathogenesis and long term consequences of the fat redistribution syndrome are incompletely understood. However such a change in body habitus has a negative impact on many patients. Despite the unparalleled success in controlling viral replication and halting the disease process that protease inhibitor containing and other HAART regimens have demonstrated, many patients have considered or have already discontinued therapy because of intolerable morphological changes. Side effects such as fat redistribution which occur at a high incidence and to such an extent of severity that they may result in discontinuation of therapy, must also be considered when deciding when to

initiate therapy. Because of the sustained durability of response associated with HAART, patients may expect to be prescribed these regimens for several years and potentially decades. Therefore understanding the syndrome and ultimately finding ways to prevent or at least manage this adverse effect are of paramount importance to the long term success of treatment for many patients.

9.5 Conclusion

Pre-marketing exposure of many agents is limited to approximately 1500 patients. Therefore post-marketing surveillance of any new drug is necessary to complete the drug's tolerability profile in clinical use. Infrequent but substantial adverse effects and in particular those whose presentation may be associated with prolonged exposure may not be recognised during pre-marketing trials and may only be identified subsequently when the drug is in routine clinical use. In pre-marketing studies, the protease inhibitors demonstrated superior antiviral efficacy as measured by surrogate markers when compared to previous anti-retroviral strategies which comprised mono or dual therapy with nucleoside analogues. Therefore, licensing of the protease inhibitors was accelerated by the FDA and other regulatory authorities to expedite the availability of these potent agents for use in routine clinical practice. Since the pre-licensing studies required were attenuated to some degree, post-marketing surveillance of drug toxicity is of paramount importance in relation to the new antiretroviral agents such as the protease inhibitors.

To detect with a power of 0.95 at least one patient with an adverse reaction which has an occurrence of 1 in 10,000, at least 30,000 patients need to be exposed to a particular agent [235]. Spontaneous post marketing surveillance schemes such as that operated by the FDA have identified a number of important adverse effects which had not been described in the pre-drug approval era, for example Diabetes Mellitus, bleeding in haemophiliacs etc.

Prolonged administration of highly active antiretroviral therapy is required to control HIV viral replication and prevent progression of HIV disease [47]. Therefore it is mandatory that the long-term complications of the composite drugs in HAART regimens be identified. Continued post-marketing surveillance in the clinical setting is needed to determine the true incidence and significance of the adverse effects of the protease inhibitors.

The table produced in this study, which summarises the published information on the tolerability of each of the protease inhibitors, was then forwarded to the relevant pharmaceutical companies for comment. Subsequent to a small number of amendments, the database was published in chart format by Mediscript Ltd. as a useful quick reference guide to the tolerability profile of the protease inhibitors [236]. This chart will be distributed to prescribers, pharmacists and other health-care professionals throughout Europe. It is envisaged that this pocket-sized guide will facilitate practitioners in the selection of antiretroviral regimens and the evaluation of potential ADRS.

CHAPTER 10

10 TOLERABILITY OF PROTEASE INHIBITORS IN AN IRISH CLINIC COHORT.

10.1 Introduction

In light of the devastating nature of untreated HIV infection and the previous dearth of effective pharmacotherapy, licensing of new antiretrovirals including the protease inhibitors has been accelerated to expedite the availability of these agents for use in routine clinical practice [33]. The licensing authorities have become increasingly reliant on surrogate marker data rather than clinical endpoints to indicate antiviral efficacy. Therefore, the mandatory pre-licensing studies have been attenuated and valuable information such as long term adverse event data may not have been available before licensure.

Much of the available information detailing efficacy and tolerability of the protease inhibitors comes from clinical trials. Aspects of drug use in the clinical setting, for example efficacy and adverse event profiles may differ from those identified in the pre-marketing studies. The antiretroviral efficacy of protease inhibitors, as demonstrated during pre-marketing exposure in clinical trials has been shown to diminish substantially during routine clinical practice. Similarly it may be expected that tolerability profiles would differ. Clinical trials frequently utilise highly selected study populations in well controlled settings. In contrast to patients in observational clinic cohorts, individuals with other pathologies or those prescribed interacting drugs are often not included in clinical trials. Study populations may be relatively homogenous with under representation of women, ethnic minorities and intravenous drug users. In addition, clinical trial participants are likely to adhere well to therapy as they are often provided with extra support as part of the study protocol.

Post-marketing surveillance of these agents is of the utmost importance to facilitate the following [237]:

- quantitative assessment of toxicity

- detection of infrequent but substantial adverse drug reactions
- assessment of long term safety/toxicity
- identification of risk factors for toxicity

Observational tolerability data from dynamic clinic cohorts is therefore useful to supplement and complement randomised clinical trial data particularly in this era of rapid drug licensure.

10.2 Aim

It was decided in 1996, coincident with the availability of the protease inhibitors, to conduct a prospective drug toxicity surveillance study in our patient cohort. Therefore, the aims of this chapter were as follows:

1. To quantify and characterise adverse drug reactions associated with protease inhibitors prescribed as part of HAART in a longitudinal observational study of an unselected clinic cohort.
2. To compare the tolerability profile of each of the protease inhibitors as determined in this study with that described in the literature.

10.3 Method

10.3.1 Data collection

A comprehensive database describing adverse drug reactions to protease inhibitors in our clinic cohort was established in the following way. All HIV-related medication prescribed to outpatients and inpatients at the time of discharge is dispensed from the satellite pharmacy which is located in the HIV outpatient clinic. Staff in the satellite pharmacy utilise a software package called Cliniscript®, which provides labels for each item dispensed. Cliniscript® also records, in a file unique to each patient, details of each item dispensed including drug, administration schedule, quantity and cost. Therefore, drug-

dispensing records from Cliniscript® can be used to determine drug regimens and duration of drug exposure. The satellite pharmacy staff provide a clinical pharmacy service including patient counselling at the outpatient clinics and on the inpatient and day wards. Tolerability data was recorded prospectively by one of these clinical pharmacists. Patient reported adverse effects were noted following routine patient counselling sessions with all inpatients and outpatients. Adverse effects recognised by the medical and nursing staff are usually reported to the clinical pharmacists. In addition, the clinical pharmacists review medical notes during each clinic visit, day ward attendance and inpatient stay. Finally, laboratory reports are reviewed subsequent to each attendance and any abnormalities noted. Therefore, information was collated on an ongoing basis by the investigator pharmacist, from a number of different sources to produce a comprehensive descriptive database of all diagnosed and patient reported clinical adverse drug reactions and laboratory abnormalities attributed to protease inhibitors during the study period.

The study period began in March 1996 when the first protease inhibitor, saquinavir$_{hgc}$ (hard gel capsule), became available in Ireland on a named patient basis. For the purposes of this analysis, data was censored on the last day of June 1999, at which time protease inhibitors available in Ireland included: saquinavir$_{hgc}$, ritonavir, indinavir, nelfinavir, amprenavir and a new soft gel formulation of saquinavir i.e. saquinavir$_{sgc}$. At the end of the study period, laboratory investigations including full blood count, renal profile, liver function tests, amylase and lipid profiles for each patient in the study were abstracted systematically from the hospital laboratory database and matched to patient and antiretroviral regimens to produce a longitudinal profile of consecutive laboratory values for each protease inhibitor exposure. Any baseline values at initiation of therapy, which fell outside of the normal range, were noted. For these exposures, only laboratory abnormalities, which had deteriorated subsequent to initiation of protease inhibitor therapy and where no other cause for deterioration was apparent, were considered as adverse drug effects.

10.3.2 Study population

Information was collected on all patient-protease inhibitor exposures during the study period. Selection of protease inhibitor therapy was individualised to the patient according to drug availability, prior antiretroviral history, known toxicity profile of the drug and patient preference. Patients, who changed therapy during the study period because of antiviral failure, non-adherence or intolerance, were studied for each drug exposure. Patients commenced on salvage regimens which included more than one protease inhibitor were excluded from the analysis, because of the difficulty of assigning causality for class related events to one drug in the combination.

10.3.3 Adverse drug reaction classification

Each adverse drug reaction (ADR) noted was graded according to severity and likely causality. The severity scale was adapted from the AIDS Clinical Trials Group (ACTG) and the Medical Research Council scoring mechanisms for grading severity of adult adverse events. This scale grades adverse drug reactions according to increasing intensity from 1 to 4. Most adverse drug reactions encountered, including all laboratory abnormalities, were included in the toxicity table and therefore graded in accordance with the relevant descriptive. For abnormalities not found in this toxicity table, the following scale was used to estimate severity (Table 10.1).

Table 10.1: Severity scale used for adverse drug reactions to the protease inhibitors, which are not included in the toxicity table.

Grade	Descriptive	Explanation
Grade 1	Mild	Transient or mild discomfort, no limitation in activity; no medical intervention/therapy required.
Grade 2	Moderate	Mild to moderate limitation in activity- some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisations possible.
Grade 4	Life-threatening	Extreme limitation in activity, substantial assistance required; substantial medical intervention/therapy required, hospitalisation or hospice care probable. Includes any clinical event considered by the clinician to be serious or life threatening.

Table 10.2: Scale used to attribute causality to adverse drug reactions to the protease inhibitors.

Grade	Explanation
Grade A	the ADR was considered to be likely due to another drug in the regimen
Grade B	the ADR could either be due to the protease inhibitor or another drug
Grade C	the ADR was considered likely due to the protease inhibitor

A comprehensive table detailing the grading of each ADR encountered in this study is included as Appendix V. Grades used to attribute causality ranged from A to C (Table 10.2). A symptom, sign or laboratory abnormality could only be considered as a grade C ADR to the protease inhibitor if it was either characteristic of this class of drugs, was reversible on discontinuation of the drug or displayed a suggestive temporal relationship to commencement of the protease inhibitor. Adverse drug reactions were classified according to time of onset. ADRs that occurred in the six weeks of therapy were classified as early onset, those that presented six weeks to six months from initiation of therapy as medium

term onset and those that occurred after more than six months of therapy as late onset. ADRs were ordered according to a system organ classification.

10.3.4 Database

An electronic database was constructed which included for each protease inhibitor exposure:

- a patient identification number,
- hepatitis B and hepatitis C infection status,
- antiretroviral regimen i.e. protease inhibitor and other antiretroviral agents,
- date of and reason for initiation of regimen,
- date of and reason for discontinuation if applicable,
- adverse drug reactions recorded,
- date of onset of adverse drug reaction,
- a severity and a causality rating.

Reasons for initiating a regimen included naïveté to therapy, failure to achieve viral suppression with previous therapy, intensification of a previous regimen or failure to comply with previous therapy. Reasons for discontinuing a regimen included failure to achieve viral suppression and consequent selection of a new regimen or intensification of the current regimen, failure to adhere to therapy and intolerance. A clinical database had been previously constructed which included patient demographics (Chapter 2). The following information pertaining to each protease inhibitor exposure was abstracted from the clinical database and merged with the adverse drug reaction database: patient age, gender and risk factor for acquisition of HIV infection.

10.3.5 Analysis

The adverse drug reaction database was analysed using the following software packages: Excel® version 7.0 (Microsoft), Access® version 7.0 (Microsoft) and JMP® version 3.2.1

(SAS Institute Inc.). The number and demographic details of the patients treated, the regimens employed, and the number and nature of the adverse drug reactions experienced were determined.

1. The overall ADR incidence rate was calculated as the number of adverse drug reactions per patient-drug exposure and also as the number of adverse drug reactions per 100 patient years of drug exposure.
2. The incidence rate for specific ADRs was expressed as the percentage of patient-drug exposures to the protease inhibitor.
3. The incidence at which each adverse drug reaction occurred in our clinic cohort was compared with adverse drug reaction incidence data from the literature previously collated as described in Chapter 9.

Pearson's Chi-squared test was used to investigate the relationship between specific patient characteristics and incidence of ADRs.

10.4 Results

Three hundred and fifty-one patients were enrolled in the study representing 625 patient-protease inhibitor exposures. Details of cohort demographics and protease inhibitor exposures are given in Table 10.3 and Table 10.4. The most commonly prescribed protease inhibitors during the study period were saquinavir$_{hgc}$ (199 exposures), ritonavir (67 exposures), indinavir (145 exposures) and nelfinavir (204 exposures). Amprenavir and saquinavir$_{sgc}$ did not become available until the end of 1998 and therefore were each prescribed in only 5 patients. Data on these protease inhibitors is included for illustrative rather than comparative purposes. Each of the protease inhibitors was prescribed at standard licensed doses except for nelfinavir. Nelfinavir was initially prescribed at the licensed dose of 750mg three times daily. Subsequent studies demonstrated similar antiviral efficacy for twice daily dosing of 1250mg. Thereafter, a number of patients were

Table 10.3: Demographic characteristics of each patient-protease inhibitor exposure.

		Total	Saquinavir$_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	Saquinavir$_{sgc}$
Number of patient drug exposures:		625 (100%)	199	67	145	204	5	5
Gender:	*male*	469 (75.0%)	146	60	114	143	1	5
	female	156 (25.0%)	53	7	31	61	4	0
Risk Group:	*homosexual*	241 (38.5%)	50	37	81	68	0	5
	heterosexual	148 (23.7%)	29	14	38	63	4	0
	haemophiliac	40 (6.4%)	15	5	11	9	0	0
	intravenous drug use	185 (29.6%)	104	11	11	59	0	0
	other	11 (1.8%)	1	0	4	5	1	0
Age at commencement of protease inhibitor (years):								
	Mean	36.81	35.9	38.1	37.4	36.8	40.0	35.5
	Range	[16.4-73.1]	[17.2-61.2]	[26.3-62.9]	[16.4-72.3]	[20.8-73.1]	[34.6-52.1]	[30.8-45.9]
Hepatitis B positive:		101 (16.1%)	42	12	21	26	0	0
Hepatitis C positive:		235 (37.6%)	121	15	29	70	0	0
Hepatitis B & C positive:		64 (10.2%)	37	5	5	17	0	0

Table 10.4: Number, duration and reasons for discontinuing protease inhibitor combination therapy.

	Total	Saquinavir$_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	Saquinavir$_{sgc}$
Number of patient drug exposures:	625	199	67	145	204	5	5
Number of patient drug exposures encountering ADRs:	528 (84.5%)	137	65	133	183	5	5
Duration of exposure (days): Mean	333.9	292.0	350.4	464.1	287.0	86.6	147.4
Range	[3-1135]	[3-1135]	[3-1134]	[16-1092]	[5-672]	[51-119]	[34-240]
Number naïve to antiretroviral therapy:	180 (28.8%)	49	15	38	78	0	0
Total discontinuing protease inhibitor:	421 (67.3%)	178	59	90	92	0	2
Reasons for discontinuing protease inhibitor therapy:							
Antiviral failure	131 (20.9%)	68	8	38	17	0	0
Non-compliance	87 (13.9%)	48	7	11	21	0	0
Intensification	25 (4.0%)	12	8	0	5	0	0
Drug interaction	7 (1.1%)	4	0	3	0	0	0
Adverse drug reaction	124 (19.8%)	28	34	24	36	0	2
Other	47 (7.5%)	18	2	14	13	0	0
Number on protease inhibitor at study closure:	204 (32.7%)	21	8	55	112	5	3

prescribed the twice-daily regimen in an attempt to maximise adherence. This regimen has subsequently been licensed in the US [238].

The majority of patients were male. The most common transmission risk groups were homosexuals and intravenous drug users. Age at commencement of protease inhibitor therapy ranged from 16.4 to 73.1 years with a mean value of 36.8 years. Of 625 drug exposures, 37.6% of drug exposures were in patients who were hepatitis C positive, 16.2% in patients who were hepatitis B positive and in 10.2% of cases patients were co-infected with hepatitis C and hepatitis B

Of 625 patient drug exposures, 528 (84.5%) resulted in ADRs. Of 351 study participants, 91.2% experienced at least one ADR to a protease inhibitor during the study period. Duration of exposure to protease inhibitors ranged from 3 to 1135 days with a mean exposure period of 333.9 days. The total duration of exposure to protease inhibitors in the study was 572.7 patient years, with the total exposure to each protease inhibitor ranging from 1.2 patient years for amprenavir, to 64.3 patient years for ritonavir to 160.4 patient years for nelfinavir. In 28.8% of exposures, patients were naïve to protease inhibitors. 204 patient-protease exposures were ongoing at study closure. The remainder discontinued protease inhibitor therapy at some point during the study period. The most common reason for discontinuing a protease inhibitor containing regimen was failure to achieve viral suppression (21.0%). 13.9% were discontinued due to non-adherence. 19.8% representing 124 of 625 drug exposures were terminated because of intolerance. Ritonavir was associated with the highest discontinuation rate (50.7%) due to intolerance.

For 625 drug exposures, 2182 ADRs were recorded giving an incidence rate of 3.5 per exposure or 380.9 per 100 patient years exposed. $Saquinavir_{hgc}$ was the best tolerated

protease inhibitor with an ADR incidence rate of 2.4 per exposure or 295.2 per 100 patient years of drug exposure. By contrast, ritonavir was associated with the highest incidence of ADRs (5.6 per exposure or 578.4 in 100 patient years of drug exposure) in addition to the highest discontinuation rate due to intolerance. Grading of these ADRs according to intensity, causality, severity and onset is shown in Table 10.5. Of 2182 ADRs recorded, 1970 were graded C i.e. most likely due to the protease inhibitor in the combination. The incidence rate of grade C ADRs was 3.1 per patient-drug exposure or 343.9 per 100 patient years exposed. Grading these C ADRs according to intensity revealed 945 grade 1, 704 grade 2, 283 grade 3 and 38 grade 4 reactions. There were no iatrogenic deaths but 13 exposures resulted in hospitalisation of the patient for management of ADRs (2%). The most common grade C ADRs, organised according to system organ classification are shown in Table 10.6. The mean time to onset of grade C ADRs was 217.7 days with a range of 1 to 1129 days. Of grade C ADRs, 22% presented within the first six weeks of therapy, 40.5% within the first six weeks to six months of therapy and 37.5% of ADRs were described as late onset i.e. occurring greater than six months from initiation of the regimen. The majority of clinical ADRs occurred early in therapy within six weeks of initiation of the protease inhibitor. The majority of laboratory abnormalities were recorded more than six months into therapy. Gastrointestinal ADRs most commonly presented in the first six weeks of therapy. Nephrolithiasis presented most commonly as a late onset ADR (59.1%). Fat redistribution syndrome also presented most commonly more than six months from initiation of therapy (70.8%).

The most common patient reported adverse drug reactions associated with protease inhibitor use were gastrointestinal. 47% of gastrointestinal effects occurred during the first six weeks of therapy. Diarrhoea was the most commonly noted ADR with an overall incidence rate of 28.3%, ranging from 11.7% with indinavir to 50.7% with ritonavir.

Table 10.5: Incidence, causality, severity and onset of adverse drug reactions to protease inhibitors.

		Total	Saquinavir$_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	Saquinavir$_{sgc}$
Number of ADRs:		2182	470	372	638	661	22	19
Incidence of ADRs per drug exposure:		3.5	2.4	5.6	4.4	3.2	4.4	3.8
Incidence of ADRs per 100 person years of drug exposure:		380.9	295.2	578.4	343.7	412.1	1845.5	941.0
Total number of Grade A ADRs:		31	7	0	6	17	1	0
Total number of Grade B ADRs:		181	27	2	34	110	3	5
Total number of Grade C ADRs:		1970	436	370	598	534	18	14
Grade I		945	207	163	289	275	2	9
Grade II		704	154	121	217	196	14	2
Grade III		283	67	73	82	56	2	3
Grade IV		38	8	13	10	7	0	0
Incidence of Grade C ADRs per drug exposure:		3.1	2.2	5.5	4.1	2.6	3.6	2.8
Incidence of Grade C ADRs per 100 person years of drug exposure:		343.9	273.9	575.3	322.1	332.9	1517.3	693.4
Time to onset of grade C ADRs (days):	**Mean**	217.7	221.5	151.8	263.9	164.8	53.9	32.1
	Range	[1-1129]	[1-1129]	[1-1057]	[2-1043]	[1-601]	[11-91]	[8-86]
Grade C ADRs according to time to onset:								
number of short term onset (< 6 weeks)		433 (22.0%)	83	128	102	104	6	10
number of medium term onset (6 weeks – 6 months)		798 (40.5%)	180	157	209	236	12	4
number of long term onset (> 6 months)		739 (37.5%)	173	85	287	194	0	0

Table 10.6: **Number of adverse drug reactions for each protease inhibitor and incidence rate per 100 patients exposed according to system organ classification.**

Gastrointestinal	Total	$Saquinavir_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	$Saquinavir_{sgc}$
Abdominal pain	40 (6.4%)	10 (5%)	7 (10.4%)	16 (11%)	7 (3.4%)	0 (0%)	0 (0%)
Amylase increased	19 (3%)	2 (1%)	3 (4.5%)	8 (5.5%)	6 (2.9%)	0 (0%)	0 (0%)
Anorexia	4 (0.6%)	1 (0.5%)	0 (0%)	3 (2.1%)	0 (0%)	0 (0%)	0 (0%)
Bloating	5 (0.8%)	0 (0%)	1 (1.5%)	0 (0%)	3 (1.5%)	1 (20%)	0 (0%)
Constipation	7 (1.1%)	2 (1%)	1 (1.5%)	3 (2.1%)	1 (0.5%)	0 (0%)	0 (0%)
Diarrhoea	177 (28.3%)	35 (17.6%)	34 (50.7%)	17 (11.7%)	86 (42.2%)	4 (80%)	1 (20%)
Dry mouth	13 (2.1%)	0 (0%)	1 (1.5%)	6 (4.1%)	6 (2.9%)	0 (0%)	0 (0%)
Dyspepsia/epigastric pain	33 (5.3%)	6 (3%)	3 (4.5%)	9 (6.2%)	14 (6.9%)	1 (20%)	0 (0%)
Faecal occult blood	1 (0.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Fat intolerance	2 (0.3%)	0 (0%)	1 (1.5%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Flatulence	12 (1.9%)	3 (1.5%)	2 (3%)	3 (2.1%)	3 (1.5%)	1 (20%)	0 (0%)
Lactose intolerance	1 (0.2%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mouth ulceration	6 (1%)	2 (1%)	0 (0%)	1 (0.7%)	3 (1.5%)	0 (0%)	0 (0%)
Nausea	144 (23%)	31 (15.6%)	43 (64.2%)	46 (31.7%)	21 (10.3%)	3 (60%)	0 (0%)
Taste perversion	17 (2.7%)	0 (0%)	7 (10.4%)	6 (4.1%)	4 (2%)	0 (0%)	0 (0%)
Thirst	5 (0.8%)	0 (0%)	0 (0%)	3 (2.1%)	2 (1.0%)	0 (0%)	0 (0%)
Vomiting	58 (9.3%)	12 (6%)	22 (32.8%)	15 (10.3%)	9 (4.4%)	0 (0%)	0 (0%)

Table 10.6 (contd.): **Number of adverse drug reactions for each protease inhibitor and incidence rate per 100 patients exposed according to system organ classification.**

Central Nervous System	Total	$Saquinavir_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	$Saquinavir_{sgc}$
Depression	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Dizziness	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Fatigue	43 (6.9%)	6 (3%)	14 (20.9%)	14 (9.7%)	7 (3.4%)	2 (40%)	0 (0%)
Headache	7 (1.1%)	2 (1%)	1 (1.5%)	1 (0.7%)	3 (1.5%)	0 (0%)	0 (0%)
Hyperaesthesia	5 (0.8%)	0 (0%)	2 (3%)	1 (0.7%)	2 (1%)	0 (0%)	0 (0%)
Insomnia	9 (1.4%)	2 (1%)	4 (6%)	1 (0.7%)	2 (1%)	0 (0%)	0 (0%)
Migraine	1 (0.2%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mood changes	9 (1.4%)	3 (1.5%)	2 (3%)	1 (0.7%)	2 (1%)	0 (0%)	1 (20%)
Nightmares	1 (0.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Perioral paraesthesia	20 (3.2%)	0 (0%)	18 (26.9%)	2 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Peripheral paraesthesia	7 (1.1%)	0 (0%)	6 (9%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Electrolyte disturbance							
Hypokalaemia	3 (0.5%)	0 (0%)	2 (3%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Hyponatraemia	3 (0.5%)	0 (0%)	0 (0%)	3 (2.1%)	0 (0%)	0 (0%)	0 (0%)

Table 10.6 (contd.): **Number of adverse drug reactions for each protease inhibitor and incidence rate per 100 patients exposed according to system organ classification.**

Dermatological	Total	$Saquinavir_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	$Saquinavir_{sgc}$
Alopecia	13 (2.1%)	2 (1%)	2 (3%)	3 (2.1%)	6 (2.9%)	0 (0%)	0 (0%)
Chelitis	6 (1%)	1 (0.5%)	2 (3%)	1 (0.7%)	2 (1%)	0 (0%)	0 (0%)
Dry lips	2 (0.3%)	0 (0%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Dry skin	9 (1.4%)	0 (0%)	0 (0%)	5 (3.4%)	4 (2%)	0 (0%)	0 (0%)
Hirsutism	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Paronychia with nail dystrophy	9 (1.4%)	1 (0.5%)	1 (1.5%)	5 (3.4%)	2 (1%)	0 (0%)	0 (0%)
Photosensitivity	10 (1.6%)	0 (0%)	1 (1.5%)	8 (5.5%)	1 (0.5%)	0 (0%)	0 (0%)
Pigment changes	9 (1.4%)	2 (1%)	0 (0%)	5 (3.4%)	2 (1%)	0 (0%)	0 (0%)
Rash	18 (2.9%)	1 (0.5%)	4 (6%)	4 (2.8%)	8 (3.9%)	1 (20%)	0 (0%)
Ear, Nose and Throat							
Cerumen increased	1 (0.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Earache	1 (0.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Hearing impairment	4 (0.6%)	1 (0.5%)	0 (0%)	2 (1.4%)	1 (0.5%)	0 (0%)	0 (0%)
Sense of smell decreased	1 (0.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Throat irritation	7 (1.1%)	0 (0%)	5 (7.5%)	2 (1.4%)	0 (0%)	0 (0%)	0 (0%)

Table 10.6 (contd.): **Number of adverse drug reactions for each protease inhibitor and incidence rate per 100 patients exposed according to system organ classification.**

Endocrine / Metabolic	Total	$Saquinavir_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	$Saquinavir_{sgc}$
Amennorrhea	3 (0.5%)	0 (0%)	1 (1.5%)	1 (0.7%)	1 (0.5%)	0 (0%)	0 (0%)
Diabetes mellitus – exacerbation	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)
Diabetes mellitus – new onset	1 (0.2%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fat redistribution syndrome	36 (5.8%)	5 (2.5%)	3 (4.5%)	15 (10.3%)	12 (5.9%)	1 (20%)	0 (0%)
Gout	1 (0.2%)	0 (0%)	1 (1.5%)	(0%)	0 (0%)	0 (0%)	0 (0%)
Hypercholesterolaemia	94 (15%)	2 (1%)	19 (28.4%)	25 (17.2%)	47 (23%)	1 (20%)	0 (0%)
Hyperglycaemia	2 (0.3%)	1 (0.5%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Hypertriglyceridaemia	245 (39.2%)	48 (24.1%)	39 (58.2%)	68 (46.9%)	87 (42.6%)	1 (20%)	2 (40%)
Hyperuricaemia	8 (1.3%)	1 (0.5%)	7 (10.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lactate dehydrogenase increased	87 (13.9%)	31 (15.6%)	8 (11.9%)	21 (14.5%)	26 (12.7%)	0 (0%)	1 (20%)
Lipomas	8 (1.3%)	1 (0.5%)	0 (0%)	4 (2.8%)	3 (1.5%)	0 (0%)	0 (0%)
Prolactinaemia	2 (0.3%)	1 (0.5%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Musculosketal							
Arthralgia	1 (0.2%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hyperreflexia	2 (0.3%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Myalgia	17 (2.7%)	5 (2.5%)	7 (10.4%)	5 (3.4%)	0 (0%)	0 (0%)	0 (0%)

Table 10.6 (contd.): Number of adverse drug reactions for each protease inhibitor and incidence rate per 100 patients exposed according to system organ classification

Genitourinary / Renal	Total	$Saquinavir_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	$Saquinavir_{sgc}$
Creatinine increased	36 (5.8%)	6 (3%)	1 (1.5%)	22 (15.2%)	5 (2.5%)	0 (0%)	2 (40%)
Dysuria	1 (0.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Erectile dysfunction	11 (1.8%)	2 (1%)	0 (0%)	5 (3.4%)	4 (2%)	0 (0%)	0 (0%)
Haematuria	5 (0.8%)	0 (0%)	1 (1.5%)	4 (2.8%)	0 (0%)	0 (0%)	0 (0%)
Libido decreased	2 (0.3%)	0 (0%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Nephrolithiasis	31 (5%)	0 (0%)	1 (1.5%)	30 (20.7%)	0 (0%)	0 (0%)	0 (0%)
Polyuria	2 (0.3%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.5%)	0 (0%)	0 (0%)
Renal colic	13 (2.1%)	1 (0.5%)	0 (0%)	12 (8.3%)	0 (0%)	0 (0%)	0 (0%)
Hepatic							
Alkaline phosphatase increased	55 (8.8%)	20 (10.1%)	13 (19.4%)	11 (7.6%)	11 (5.4%)	0 (0%)	0 (0%)
Alanine transferase increased	66 (10.6%)	31 (15.6%)	14 (20.9%)	19 (13.1%)	2 (1%)	0 (0%)	0 (0%)
Aspartate transferase increased	152 (24.3%)	60 (30.2%)	12 (17.9%)	30 (20.7%)	49 (24%)	0 (0%)	1 (20%)
Bilirubin increased	122 (19.5%)	25 (12.6%)	11 (16.4%)	75 (51.7%)	11 (5.4%)	0 (0%)	0 (0%)
γ-glutamyl-transferase increased	145 (23.2%)	46 (23.1%)	20 (29.9%)	26 (17.9%)	48 (23.5%)	0 (0%)	5 (100%)
Hepatic failure	1 (0.2%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hepatomegaly	1 (0.2%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Jaundice	4 (0.6%)	1 (0.5%)	1 (1.5%)	1 (0.7%)	1 (0.5%)	0 (0%)	0 (0%)

Table 10.6 (contd.): **Number of adverse drug reactions for each protease inhibitor and incidence rate per 100 patients exposed according to system organ classification.**

Haematological	Total	$Saquinavir_{hgc}$	Ritonavir	Indinavir	Nelfinavir	Amprenavir	$Saquinavir_{sgc}$
Bleeding in haemophiliacs	9 (1.4%)	5 (2.5%)	2 (3%)	1 (0.7%)	1 (0.5%)	0 (0%)	0 (0%)
Neutropenia	1 (0.2%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Opthalmological							
Dry eyes	5 (0.8%)	2 (1%)	0 (0%)	3 (2.1%)	0 (0%)	0 (0%)	0 (0%)
Photophobia	1 (0.2%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Systemic							
Alcohol tolerance reduced	7 (1.1%)	0 (0%)	6 (9%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Body odour	2 (0.3%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Breast pain	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Fever	3 (0.5%)	0 (0%)	3 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Flu-like symptoms	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Hypertension	3 (0.5%)	1 (0.5%)	0 (0%)	1 (0.7%)	1 (0.5%)	0 (0%)	0 (0%)
Leg oedema	2 (0.3%)	1 (0.5%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Night sweats	2 (0.3%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Parotid swelling	6 (1.0%)	2 (1%)	0 (0%)	3 (2.1%)	1 (0.5%)	0 (0%)	0 (0%)
Sub mandibular node swelling	3 (0.5%)	2 (1%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Weight gain	5 (0.8%)	4 (2%)	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Weight loss	21 (3.4%)	4 (2%)	3 (4.5%)	6 (4.1%)	8 (3.9%)	0 (0%)	0 (0%)

Flatulence was noted with each drug with an overall incidence rate of 1.9%. Nausea was reported in 23.0% of protease inhibitor exposures, ranging from 10.3% with nelfinavir to 64.2% with ritonavir. Vomiting occurred at an overall incidence rate of 9.3% ranging from 4.4% with nelfinavir to 32.8% with ritonavir. Abdominal pain was a commonly reported ADR (6.4%) and dyspepsia occurred at a rate of 5.3%. Dry mouth and taste perversion were reported in association with ritonavir, indinavir and nelfinavir only.

Distorted liver function tests, which were the most commonly encountered laboratory abnormalities, occurred during 255 drug exposures. In 53 of these protease inhibitor exposures, patients exhibited some abnormality in liver function prior to initiation of protease inhibitor therapy. Increased liver function tests were most commonly associated with saquinavir$_{hgc}$. However the greatest incidence of elevated bilirubin was in association with indinavir. Jaundice occurred in 4 patients, one each on saquinavir$_{hgc}$, ritonavir, indinavir and nelfinavir. Other laboratory abnormalities included increased lactate dehydrogenase, which occurred at an overall incidence of 13.9%. Elevation in serum creatinine was also most commonly associated with indinavir. Hypercholesterolaemia and hypertriglyceridaemia occurred at overall rates of 15.0% and 39.2% respectively and were most commonly associated with ritonavir at rates of 28.4% and 58.2%.

Endocrine or metabolic abnormalities included fat redistribution syndrome, which occurred in 5.8% of patient-drug exposures. Symptoms of fat redistribution syndrome included central adiposity, breast enlargement in women, gynecomastia, peripheral wasting and lipoma. One patient developed new-onset diabetes mellitus, one suffered an exacerbation of underlying diabetes and hyperglycaemia was noted in 2 other patients. Drug specific adverse drug reactions included nephrolithiasis and renal colic in association with indinavir and perioral and peripheral paraesthesia in association with ritonavir. Eleven patients

reported erectile dysfunction subsequent to initiation of protease inhibitor therapy. Increased bleeding was reported for nine patient-drug exposures (18.1 per 100 haemophiliac-patient years). Seven patients reported a reduced tolerance to alcohol subsequent to initiation of protease inhibitor therapy. Nine patients reported changes in pigmentation and ten reported photosensitivity. Thirteen patients reported alopecia, which included loss of limb hair and loss of head hair in women. Paronychia with nail dystrophy was reported in nine patients. Rash occurred at an overall incidence rate of 2.9%, most commonly associated with ritonavir (6.0%). Fatigue was reported in association with all drugs except saquinavir$_{sgc}$ at an overall rate of 6.9%.

10.5 Discussion

All antiretroviral patient exposures during the period under review, which included one protease inhibitor, were1 included in this study. In common with many other studies, the majority of patients treated were homosexual men. Nevertheless, in this study women and intravenous drug users were also well represented. Furthermore, a considerable proportion of exposures included patients co-infected with hepatitis B and C. Therefore, this study constitutes the evaluation of tolerability of the protease inhibitors in a real life clinical cohort in contrast to the highly selected patient groups studied in clinical trials [239].

10.5.1 Gastrointestinal effects

Gastrointestinal disturbances are the most frequently encountered adverse events with the protease inhibitors. For the most part, gastrointestinal toxicity occurs early in the treatment course and is self limiting in nature. Nausea was reported in 23% of all protease inhibitor exposures and was responsible for drug discontinuation in 29 patients. However in the majority of cases (54.9%), nausea occurred early in the treatment course and was transient in nature, resolving spontaneously or with adjuvant anti-emetic therapy. Diarrhoea was the

most prominent gastrointestinal side effect noticed with nelfinavir occurring during 42.2% of exposures to the drug. Amongst patients who complained of diarrhoea, 47.1% presented within the first six weeks of therapy. In most patients, diarrhoea was transient (27.9%) or could be controlled easily with the antidiarrhoeal agent loperamide (66.3%). Amongst patients prescribed nelfinavir, 2.5% discontinued the drug due to intransigent diarrhoea.

10.5.2 Central nervous system effects

Perioral and peripheral paraesthesia occurred predominantly in association with ritonavir. These adverse drug reactions were reported as drug specific effects of ritonavir in pre-marketing studies with incidences between 2 and 10% [43, 44]. In our cohort, the incidence of peripheral paraesthesia associated with ritonavir was similar to that reported in the literature (9.0%), whereas the incidence of perioral paraesthesia was considerably higher at 26.8%. These adverse effects are usually transient in nature and resolve spontaneously within the first month of therapy. However, 6 of 18 patients in our cohort, who experienced perioral paraesthesia, discontinued therapy citing this side effect as one of the reasons for intolerance of this drug. There are no known pharmacological interventions that ameliorate these side effects. However, some benefit may be derived from alteration of dosing schedule.

A few months after ritonavir became available in our clinic, it was noted that the drug appeared to be associated with considerable toxicity problems most notably nausea, vomiting, diarrhoea, peripheral and perioral paraesthesia. Of the first seventeen patients prescribed ritonavir, 70% of those reporting adverse events indicated the onset of symptom 2 hours after a dose and lasting approximately 4 hours, thereby suggesting dose related toxicity. Our group postulated that alteration of the dosing schedule from 600mg twice daily to 300mg four times daily, which would result in diminished peak concentrations of

ritonavir, might be associated with improvement in dose related toxicity [240]. Based on a knowledge of the pharmacokinetic parameters of the drug, plasma ritonavir concentration time profiles were constructed which suggested that four times daily dosing would maintain the trough value of ritonavir above 2.1 $\mu g\ ml^{-1}$, the 90% effective concentration (EC_{90}), thereby ensuring antiviral efficacy was not compromised. A subsequent pharmacokinetic investigation and an efficacy and toxicity surveillance study validated this concept. Hereafter, a policy of switching patients who complained of apparent dose related toxicity to 4 times daily dosing was adopted. Adherence to the new schedule may be compromised by the frequency of daily dosing. Nevertheless, this strategy provides a means for patients who otherwise might have discontinued the drug to benefit from this potent antiviral agent.

The protease inhibitors most commonly associated with fatigue are ritonavir and indinavir at incidence rates between 2 and 10% [90, 168]. Our study reports a similar incidence of fatigue in association with indinavir but an elevated incidence of 20.9% associated with ritonavir. Both perioral paraesthesia and fatigue due to ritonavir were documented to occur more often in our cohort than had been previously reported.

Six patients prescribed ritonavir and one patient prescribed indinavir reported a decreased tolerance and a sense of heightened intoxication with alcohol subsequent to initiation of protease inhibitor therapy. This phenomenon has not been reported to date either as an adverse effect or a drug interaction.

10.5.3 Hepatic effects

Of 625 patient-drug exposures included in the study, distortion of at least one liver function test occurred in 40.8%. According to previous reports, increased alanine transferase (ALT) and aspartate transferase (AST) occurred in 2-10% of patients

prescribed ritonavir, saquinavir and indinavir, and less than 2% prescribed nelfinavir [90, 166, 168-170]. In our series, increased ALT occurred at rates of 10-20% of patients prescribed ritonavir, saquinavir$_{hgc}$ and indinavir and in less than 2% prescribed nelfinavir. Increased AST occurred at rates substantially greater in patients prescribed ritonavir, saquinavir$_{hgc}$, indinavir and nelfinavir, than those previously reported (17.9%, 30.2%, 20.7% and 24.0% respectively). Increased gamma-glutamyl transferase (GGT) has been reported in greater than 20% of patients prescribed ritonavir, 2-10% of patients prescribed saquinavir and in less than 2% receiving nelfinavir but has not been reported in association with indinavir [90, 166, 169, 170]. We found increased GGT in 17.9% of patients prescribed indinavir and in greater than 20% of patients prescribed ritonavir, saquinavir$_{hgc}$ and nelfinavir (29.8%, 23.1% and 23.5% respectively). The incidence of abnormal liver function tests was much higher in our cohort than previously reported.

Increased alkaline phosphatase has been reported previously in less than 2% of patients prescribed ritonavir, saquinavir and nelfinavir, and has not been reported in association with indinavir [90, 166, 169, 170]. However, in our cohort, increased alkaline phosphatase occurred in 2-10% of patients prescribed saquinavir$_{hgc}$, nelfinavir and indinavir and in 19.4% of patients prescribed ritonavir. Increased bilirubin is reported in the literature at rates less than 2% in association with saquinavir and ritonavir, not at all with nelfinavir and at an incidence of 10 - 20% with indinavir. In our study, 12.6% and 16.4% of patients prescribed saquinavir$_{hgc}$ and ritonavir and 5.4% of patients receiving nelfinavir had elevated bilirubin levels. More than half of all patients prescribed indinavir (51.7%) demonstrated increased bilirubin. This iatrogenic indirect hyperbilirubinaemia appears not to have any clinical consequences or sequelae. Jaundice was reported in our cohort in only four patients, one each prescribed saquinavir$_{hgc}$, ritonavir, indinavir and nelfinavir. Hyperbilirubinaemia in association with indinavir is dose related occurring with greater

frequency when total daily indinavir dosage exceeds 2.4g [168]. In our study, a trend towards an increased incidence of indinavir related hyperbilirubinaemia was noted in patients co-infected with hepatitis B and/or hepatitis C than in the uninfected cohort (56% versus 50%).

One possible explanation for the greater incidence of abnormal liver function tests in our cohort than reported in other studies may be the high incidence of co-infection with hepatitis B and/or hepatitis C amongst our patients. The incidence of at least one abnormal liver function test in patients co-infected with either hepatitis B or C or both was statistically significantly higher at 48% in contrast to 35% in patients who were negative for either infection ($p=0.001$). Infection with hepatitis B or C may result in varying degrees of liver dysfunction. The protease inhibitors are principally metabolised by cytochrome P450 iso-enzymes. Patients with liver dysfunction may potentially have diminished drug metabolising ability leading to increased serum levels of protease inhibitors [241]. Therefore, patients co-infected with hepatitis B and/or C may be subject to an increased incidence of adverse effects including distortion of liver function tests. Alternatively, HAART may result in immune reconstitution and restoration of the anti-hepatitis B and C immune responses. It has been suggested that elevation of liver function tests subsequent to the introduction of protease inhibitor containing regimens may therefore reflect immune reconstitution rather than drug induced toxicity.

10.5.4 Genitourinary effects

Nephrolithiasis was described in pre-marketing studies of indinavir to occur at an incidence of 4%. Post-marketing surveillance studies have revealed a higher incidence rate of nephrolithiasis of 9% [192]. In our patient group, 30% of patients prescribed indinavir presented with symptoms of nephrolithiasis with six patients presenting on two occasions.

28.6% of these patients presented with renal colic only. In the remainder, the diagnosis was made by either diagnostic imaging or by identification of crystals on urinalysis. All responded promptly to aggressive hydration. Patients co-infected with hepatitis B and/or hepatitis C were noted to have a statistically substantial higher incidence of nephrolithiasis at a rate of 42% in contrast to a rate of 23% in the remainder of the cohort (p=0.02). This finding may possibly be explained by hepatitis related reduction in hepatic drug clearance and subsequent increased plasma indinavir concentration leading to increased incidence of nephrolithiasis. Brodie *et al* have previously noted an increased incidence of nephrolithiasis in hepatitis C infected haemophiliac patients prescribed indinavir [242].

Renal insufficiency has also been reported in association with indinavir use. Indinavir related crystalluria and nephrolithiasis may lead to renal insufficiency and even acute renal failure with obstructive nephropathy [178-180]. The incidence of renal insufficiency in patients prescribed indinavir, as defined by increased serum creatinine greater than the upper limit of normal (125 μmol/L) was 15.2% in our cohort. Elevated serum creatinine occurred in 20% of patients presenting with nephrolithiasis. However, 66.6% of cases of increased creatinine were asymptomatic and occurred independently of any clinical sign of nephrolithiasis. Renal toxicity of indinavir is associated with substantial morbidity and may limit the clinical utility of this effective antiretroviral agent. During the study period ten patients (6.8%) presenting with nephrolithiasis required hospitalisation for analgesia and aggressive hydration to dissolve indinavir crystals. Five patients (3.4%) discontinued indinavir therapy because of nephrolithiasis. One patient, who had no clinical signs of nephrolithiasis, discontinued because of a grade 3 increase in serum creatinine. Nephrolithiasis presented as a late onset adverse drug reaction in the majority of cases (59.1%) i.e. greater than 6 months into therapy. Advice to patients regarding the

maintenance of an increased fluid intake to minimise the risk of nephrolithiasis should be reiterated throughout the treatment course.

Nephrolithiasis appears to be a drug specific effect primarily associated with indinavir, but has also been reported at incidences less than 2% in association with saquinavir, ritonavir and nelfinavir [90, 170, 186]. In this study, one patient prescribed ritonavir presented with nephrolithiasis. Increased serum creatinine concentration was noted in one case of exposure to ritonavir, five cases of exposure to nelfinavir and six cases of exposure to saquinavir$_{hgc}$. In each of these cases, elevation of serum creatinine was categorised as grade 1 or 2 i.e. up to 375μmol/L and did not require discontinuation of protease inhibitor therapy. There have been some reports in the literature of renal insufficiency associated with ritonavir, and ritonavir combined with saquinavir [184, 185, 187, 188]. In one series of 87 patients prescribed ritonavir in combination with two nucleoside analogues, the incidence of renal insufficiency was 14% [184]. The mechanism by which protease inhibitors other than indinavir might cause renal insufficiency is unknown.

There have been some reports of erectile dysfunction as a consequence of protease inhibitor therapy in the literature [243, 244]. An overall incidence of almost 2% was observed in our patient cohort. Five patients prescribed indinavir, four prescribed nelfinavir and two prescribed saquinavir$_{hgc}$ reported erectile dysfunction subsequent to initiation of protease inhibitor therapy. The mechanism of this ADR is unknown.

10.5.5 Dermatological effects

There have been case reports of alopecia in patients prescribed indinavir [175, 245]. In our study, alopecia was reported in 2.1% of exposures to indinavir. Furthermore, this ADR occurred in 3.0% of patients prescribed ritonavir, 2.9% of patients prescribed nelfinavir and 1% of patients prescribed saquinavir$_{hgc}$. Patients reported loss or thinning of body hair

and thinning of head hair in women, subsequent to initiation of protease inhibitor therapy. Amongst patients with this ADR, 30.7% noticed onset during the first six weeks of therapy. Four patients discontinued protease inhibitor therapy due to this side effect (2 ritonavir, 1 saquinavir$_{hgc}$, and 1 indinavir). Previous attempts to explain the mechanism of this side effect included a hypothesis that protease inhibitors interfere with retinoid metabolism [226]. One author has suggested that this is a drug specific phenomenon peculiar to indinavir [175]. However we have noted this complication in conjunction with each of the frequently used protease inhibitors. Of interest, a single patient prescribed nelfinavir reported hirsutism subsequent to initiation of therapy.

Paronychia with nail dystrophy occurred in 1.4% of all patient-protease inhibitor exposures, but was most commonly associated with indinavir (3.4%) which is similar to results presented by Bouscarat *et al* who reported a 4% incidence of paronychia in patients taking indinavir [176]. There have previously been case reports of paronychia in association with other protease inhibitors [177]. In our study, paronychia with nail dystrophy was also reported in one patient on saquinavir$_{hgc}$, one patient on ritonavir and two patients prescribed nelfinavir. As for alopecia, it has been suggested that interference with retinoid metabolism may be the mechanism of this adverse drug reaction [226].

Exposures to protease inhibitor therapy appear to alter the dermatological response to sunlight. Prior studies have reported photosensitivity in less than 2% of patients prescribed ritonavir and saquinavir and case reports of pigmentation change in patients on indinavir [90, 168, 170]. One patient on ritonavir and no patients on saquinavir$_{hgc}$ demonstrated photosensitivity, however 5.5% of those prescribed indinavir did. Pigmentation changes were reported in patients on saquinavir$_{hgc}$, indinavir and nelfinavir at rates of 1%, 3.4% and

1% respectively. At our clinic, patients prescribed protease inhibitors are routinely advised on sun protection in particular if travelling to sunnier climates than Ireland.

Product information suggests that rash may occur at incidences of between 10 and 20% with amprenavir and indinavir, between 2 and 10% with saquinavir and nelfinavir and in less than 2% of patients exposed to ritonavir [90, 165, 166, 168-170]. Rash occurred in our cohort in association with each protease inhibitor. Of note, amongst patients prescribed indinavir, rash occurred at a lower rate than represented in the literature i.e. 2.8% but presented at a higher rate of 6% in patients prescribed ritonavir. Seven patients discontinued protease inhibitor therapy because of rash.

10.5.6 Haematological effects

The FDA issued a warning to healthcare providers in November 1996 regarding a possible increased risk of bleeding in haemophiliacs taking protease inhibitors [246]. During the study period, 25 haemophiliac patients were prescribed protease inhibitors resulting in 40 patient-drug exposures. In view of the FDA warning, all patients were counselled to report any signs of increased bleeding tendency. In a nested study, we examined patient clotting factor requirements in the first twenty patient-protease inhibitor exposures, for the six months prior to and post commencement of protease inhibitors [247]. There was no statistically significant difference in the number of bleeding episodes requiring factor replacement therapy before and after initiation of protease inhibitor therapy. However in this longitudinal surveillance study, 22.5% of patients reported an increased tendency to bleed, which they attributed to their antiretroviral therapy. Individual patients reported haemorrhages at sites, which were unusual for them, for example dorsum of the foot and the forearm but which responded well to standard factor replacement therapy. One patient discontinued therapy because of his perception that saquinavir$_{hgc}$ therapy was causing an

increased tendency to bleed. In another centre, ten of seventeen patients reported increased bleeding or changes in bleeding pattern in the first six months of therapy[189]. To date the causal link between the protease inhibitors and increased bleeding tendency in haemophiliacs has not been proven. However this series does add some additional evidence, albeit anecdotal, of the existence of such a relationship.

Neutropenia has been reported in the literature at rates of less than 2% in patients receiving saquinavir and ritonavir, and at rates between 2 and 10% in patients receiving nelfinavir or indinavir [90, 166, 168-170]. One case of grade C neutropenia was reported in our cohort. The causal link to saquinavir$_{hgc}$ was established when recurrent grade 3 neutropenia persisted despite sequential substitution of each of the other agents in this patient's regimen. Substitution of saquinavir$_{hgc}$ with indinavir resulted in resolution of neutropenia within 6 weeks.

10.5.7 Endocrine effects

Hyperuricaemia has been reported to occur in 2-10% of patients prescribed ritonavir and less than 2% of those prescribed saquinavir [90, 170]. In our study, one patient receiving saquinavir$_{hgc}$ and seven patients (10.4%) receiving ritonavir had elevated uric acid levels. However, hyperuricaemia resulted in clinical presentation of gout in only one patient prescribed ritonavir. This patient was managed acutely with non-steroidal anti-inflammatory agents and then commenced on low dose allopurinol therapy without further incident.

Hypercholesterolaemia has been reported to occur at incidences of greater than 20% in patients prescribed ritonavir, indinavir and nelfinavir [194-196]. One retrospective review reported an incidence of 2.8% in patients prescribed saquinavir$_{hgc}$ as sole protease inhibitor

[194]. Another study, which prospectively followed 38 consecutive patients prescribed saquinavir$_{sgc}$, reported a 7.9% incidence of cholesterol elevated above the US National Cholesterol Education Program guidelines limit for intervention of 6.5mmol/L [197]. This suggests that the low incidence of hypercholesterolaemia apparent with the hard gel capsule may be due to poor bioavailability of this formulation. In our study, hypercholesterolaemia exceeded 20% in patients prescribed ritonavir and nelfinavir. However, only 17.2% of those prescribed indinavir and 1% of those prescribed saquinavir$_{hgc}$ had elevated cholesterol levels.

Hypertriglyceridaemia has previously been reported in greater than 20% of those prescribed ritonavir, nelfinavir and indinavir, and in 7.9% of those prescribed saquinavir$_{sgc}$ [195-197]. In our cohort, greater than 20% of patients, regardless of protease inhibitor prescribed, demonstrated hypertriglyceridaemia. 24.1% of those prescribed saquinavir$_{hgc}$ and 58.2%, 46.9% and 42.6% of those prescribed ritonavir, indinavir and nelfinavir respectively had elevated triglycerides. However in our study, albeit in common with most other studies, the triglyceride levels were routine samples and therefore most likely non-fasting. Measurement of fasting levels would be required to determine a true incidence and degree of hypertriglyceridaemia associated with these agents. Case reports of pancreatitis associated with increased triglycerides and vascular complications associated with elevated cholesterol have been documented in patients prescribed protease inhibitors [199-202, 248-250]. Two cases of pancreatitis occurred in this patient cohort during the study period. However in each case causality was attributed to didanosine which had been co-prescribed as part of the antiretroviral regimen. No atherogenic vascular complications were definitively attributed to protease inhibitor use in our cohort.

A number of cross-sectional studies have reported fat redistribution in greater than 20% of patients prescribed ritonavir, indinavir and nelfinavir and there have also been case reports in patients prescribed saquinavir [220, 221, 224]. In our cohort fat redistribution syndrome was most commonly reported in association with indinavir (10.3%) while a lower incidence was noted in association with nelfinavir, ritonavir and saquinavir$_{hgc}$ i.e. 5.9%, 4.5% and 2.5% respectively. DeLuca *et al* have previously reported an increased relative risk (2.37, p=0.03) of fat redistribution associated with indinavir compared with the other protease inhibitors after a median treatment duration of 28 weeks [225]. As expected, the lowest incidence was in patients prescribed saquinavir$_{hgc.}$ The poor bio-availability of this protease inhibitor may contribute somewhat to the lower associated incidence of fat redistribution. Although ritonavir was associated with the highest incidences of elevated cholesterol and triglycerides in our cohort, the incidence of fat redistribution was only 4.5%. It has been noted that the incidence and severity of lipodystrophy increase with duration of protease inhibitor therapy. The incidence of fat redistribution in our patients who remained on ritonavir therapy for longer than 12 months was 8.7%. It is worth noting that diagnosis of fat redistribution syndrome was made on the basis of patient self reported history and clinical examination. Radiological techniques or arthropometric measurements were not employed.

In June 1997, the FDA issued a warning to healthcare workers of risk of new onset diabetes mellitus and exacerbation of existing diabetes mellitus in HIV-infected patients receiving protease inhibitor therapy [210]. A number of cross sectional studies have reported impaired oral glucose and peripheral insulin tolerance [212, 213, 215]. In our cohort, new onset diabetes mellitus was diagnosed in one haemophiliac patient taking saquinavir$_{hgc}$. One patient was hospitalised following exacerbation of his pre-existing diabetes mellitus subsequent to prescription of amprenavir.

Increased lactate dehydrogenase (LDH) has been reported in less than 2% of those prescribed ritonavir and nelfinavir and has not been reported in association with the other protease inhibitors [90, 166]. We noted an overall incidence of increased LDH in 13.9% (11.9% to 15.6%) of patients prescribed saquinavir$_{hgc}$, ritonavir, indinavir and nelfinavir. This increase in LDH appears to occur without clinical sequelae. The mechanism for its occurrence and the reason for the high incidence in this cohort are unknown.

10.5.8 General Discussion

Saquinavir$_{hgc}$ was the best tolerated of the protease inhibitors in this study. One explanation may be the low bio-availability of the hard gel formulation (4%) leading to low drug exposure and diminished dose related toxicity [169]. The newer soft gel formulation provides a four-fold increase in bio-availability and is reported in the literature to have an enhanced toxicity profile [170]. The small number of patients prescribed saquinavir$_{sgc}$ in our study precluded a comparison of the tolerability profile of the two formulations. Ritonavir was associated with the highest incidence of adverse drug reactions and the greatest number of discontinuations of therapy due to intolerance, despite slow dose escalation, intensive counselling and initiation of all patients on the more palatable capsule formulation. Gastrointestinal toxicity, most commonly nausea and diarrhoea was the most common cause of discontinuation of ritonavir due to intolerance. In October 1998, due to technical manufacturing difficulties, the capsule formulation was withdrawn from the market forcing patients to substitute ritonavir liquid. The unpleasant taste of the liquid formulation resulted in another two patients discontinuing ritonavir therapy due to gastrointestinal side effects.

The toxicity profile of the protease inhibitors is substantial with an overall incidence of 343.9 adverse drug reactions per 100 patient years of drug exposure. Approximately 50% of these were grade 1 ADRs resulting in minimal discomfort. Nevertheless, side effects are a considerable cause of morbidity in these patients. 20% of potentially highly effective protease inhibitor containing regimens were discontinued due to intolerance. 2% of patients were hospitalised for management of adverse drug reactions. Although gastrointestinal toxicity to the protease inhibitors including nausea, vomiting and diarrhoea occur most commonly in the first six weeks of therapy, other ADRs present more frequently later on. It is important for practitioners to continuously monitor for clinical signs and laboratory abnormalities through out the treatment course.

This unselected cohort may not provide definitive adverse drug reaction incidence rates. It does however provide an important means to determine the profile and magnitude of adverse effects to protease inhibitors in a cohort in which women, intravenous drug users and patients co-infected with hepatitis B and hepatitis C are represented at higher proportions than in many of the clinical trial settings. Furthermore, it highlights how toxicity profiles may differ between clinical trials and the real life clinical setting. In our study the higher than expected incidence rates of distorted liver function tests and nephrolithiasis may reflect dose related intensity of adverse drug reactions in patients who because of compromised liver metabolism are exposed to higher serum levels of these agents. Therefore close surveillance for these ADRs is advisable when treating patients co-infected with hepatitis B and/or C. The incidence of fat redistribution syndrome noted in our cohort is substantially lower than the rate recorded in the literature. This may reflect a shorter overall duration of exposure of our cohort to HAART as a consequence of the later availability of these agents in Ireland than in other countries, for example USA and Australia. In addition, prospective toxicity surveillance studies such as this one provide

valuable information on the safety of these agents in selected populations including haemophiliacs who would not routinely be well represented in clinical trials.

At present, antiretroviral therapy once initiated is life long. Good adherence is mandatory to avoid the development of resistance mutations which limit drug antiviral efficacy and which may limit the potency of subsequent agents due to cross resistance [161]. Drug toxicity has been identified as one of the factors predisposing to poor adherence[161]. Conversely, extensive patient knowledge of aspects of their medication including purpose, mechanism of action, administration schedule and tolerability profile has been shown to impact positively on adherence[161]. The clinical pharmacist has an important role in patient education to allow patients to make informed decisions about initiating and adhering to therapy. The results of this study, which takes account of the impact of local demographics and co-morbidities, facilitate the provision of comprehensive patient information outlining the likely incidence and nature of adverse drug reactions in the Irish clinical setting.

10.6 Conclusion

The protease inhibitors exhibit a considerable toxicity profile. However, these antiretroviral agents, as constituents of combination therapy, have demonstrated unparalleled antiviral efficacy in comparison to earlier strategies [19]. Therefore, analysis of the risk-benefit ratio allows inclusion of these valuable agents in the antiretroviral armamentarium. While the accelerated approval process of many new HIV medications has increased patient access to life-prolonging therapies, it has also limited the availability of adverse drug event data at time of marketing. Post marketing surveillance of these agents has revealed a number of idiosyncratic drug side effects and also the presentation of known ADRs at a higher incidence than previously noted. The incidence of nephrolithiasis

is considerably higher than found in the pre-marketing studies and has been linked to environmental conditions and duration of exposure. Increased tendency to bleed in haemophiliacs, glucose intolerance and fat redistribution syndrome are phenomena linked to protease inhibitor exposure that have emerged post licensure. Prolonged administration of HAART is required to control HIV viral replication and prevent progression of HIV disease [47]. As yet the longest period of exposure to protease inhibitors has not exceeded six years. The expectation of greatly increased life expectancy associated with life long therapy with highly active antiretroviral therapy, underscores the importance of continuous post marketing surveillance to further define the ADR profile of these agents over longer exposure times.

CHAPTER 11

11 DISCUSSION

11.1 Introduction

This thesis constitutes a unique contribution to our understanding of pharmacoeconomics and pharmacoepidemiology of HIV infection at both a national and international level. Prior to commencement of this study, the unparalleled antiretoviral efficacy of HAART was becoming apparent[12, 13, 48, 66]. Palella *et al.* had demonstrated that the adoption of HAART as standard of care coincided with statistically significant reduction in HIV-related opportunistic diseases (Figure 11.1).

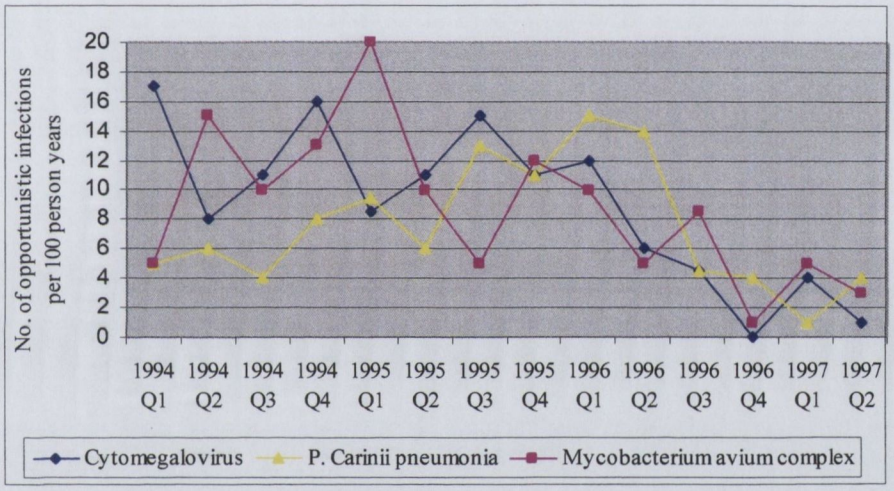


Figure 11.1 **Rates of opportunistic disease among HIV patients with CD4 cell counts less than 100 x 10^6/L according to calendar quarter from January 1994 through June 1997. HAART was first introduced in the first quarter of 1995.** Adapted from Palella et al. [12].

At our centre, a doubling in outpatient expenditure on HIV-related medication from approximately IR£0.5m in 1995 to IR£1m in 1996 was noted and presumed attributable to the introduction of expensive HAART regimens during 1996 (Figure 11.2). It appeared intuitive that a decrease in HIV-related morbidity would translate into decreased expenditure on pharmacotherapy of opportunistic disease and reduction in hospitalisation costs, thereby offsetting the high acquisition cost of HAART to some extent. This thesis which analysed the impact of HAART on the pharmacoepidemiology and

pharmacoeconomics of HIV infection in Ireland revealed a number of interesting and sometimes counterintuitive observations.

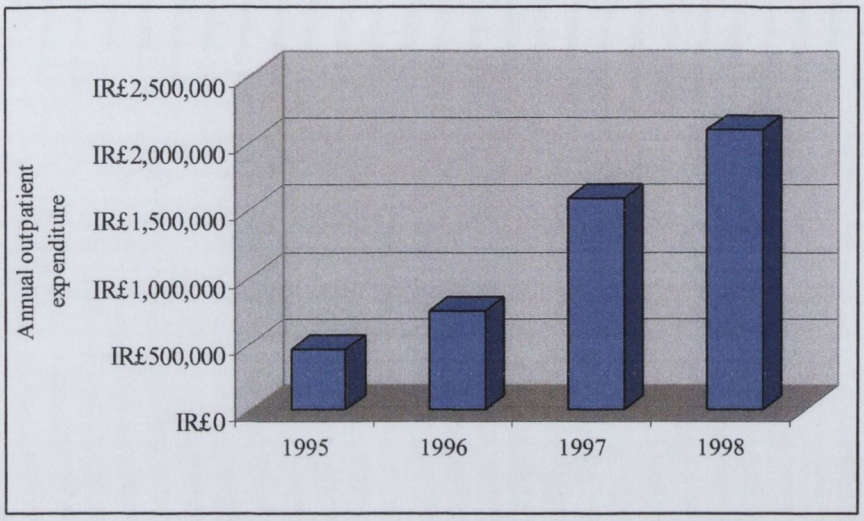


Figure 11.2 Annual outpatient expenditure on HIV-related medication.

11.2 Sustained improvement in immunological status of the active cohort.

The strong correlation observed between CD4 cell count and time deserves close analysis. Examination of the median CD4 cell count of the active cohort each quartile of the period under review revealed a striking linear relationship ($p<0.0001$, $R^2=0.948$, median CD4= 95.7 + 13.3 contact quarter). Therefore, a sustained improvement in immunological function was observed throughout the first 5 quartiles of the study prior to the availability of HAART, in addition to further sustained improvement in each quartile subsequent to HAART through to the end of the study period. A possible explanation is that in the pre-HAART era, improvement was due to a switch from monotherapy to dual combination therapy and to the availability of lamivudine in the third quartile of 1995. Further improvements subsequent to the adoption of HAART may be due to the ongoing availability of new potent antiretroviral agents with improved administration schedules, tolerability or resistance profiles throughout the study period. In addition, increased physician experience has previously been shown to correlate with improved therapeutic outcomes[70].

Plasma HIV RNA measurement only became available in the third quartile of 1996 after the introduction of HAART. Nevertheless, a sustained improvement in the virological profile of the cohort similar to the improvement in the immunological profile was noted from the availability of the test through to the end of the study period ($p<0.0001$, $R^2=0.81$, median log viral load = 5.09 + 0.12 contact quarter). These changes noted in surrogate markers of disease progression and coincident changes in clinical endpoint data are obviously complex and may be driven by factors that are incompletely understood at this point.

11.3 Pharmacoeconomic assumptions

The discipline of pharmacoeconomics assesses the benefits derived from new therapeutic options by determining changes in clinical endpoints and expenditure or resource consumption. Frequently, however, the relevant individual patient data is time consuming, difficult and occasionally impossible to collect. Pharmacoeconomics is not an exact science in that deficiencies in the availability of information are usually compensated for by reliance on assumptions considered reasonable by experts in the field. Such assumptions are used to model likely clinical outcomes and resource consumption.

In conducting this study reliance on assumptions rather than detailed data collection was avoided for two reasons. Firstly, because of the dynamic nature of HIV disease, assumptions relating to HIV disease progression and resource consumption, even if validated in a clinical cohort are quickly outdated in an environment where therapeutic interventions and resultant outcomes change rapidly at a rate unprecedented in many other clinical specialities. Secondly, as this was the first cost of illness study to be carried out in Ireland there existed a relative dearth of detailed and reliable cost data. Prior to this work, no assumptions in relation to resource consumption had been validated in the Irish setting.

Therefore, the approach adopted to data collection on clinical endpoints and resource utilisation was as comprehensive and detailed as possible. Assumptions were not employed to generate data unless unavoidable. However, this approach facilitated an evaluation and validation of a number of possible assumptions, which may prove useful and reliable in future pharmacoeconomic work in this country as outlined in the following sections 11.4, 11.5 and 11.6. In addition, the detailed nature of the data collection allowed a more in depth analysis when results appeared counterintuitive.

11.4 Pharmacoeconomics of opportunistic disease

Following an examination of the data collected during this study, it becomes apparent that simplistic pharmacoeconomic evaluation in HIV disease should be avoided. HIV disease is in fact a constellation of numerous distinct clinical entities and therefore an understanding of the pathophysiology of the disease predicts that analysis in this area might be complex. Substantial decreases in the incidence of MAC, toxoplasmosis, oesophageal candidiasis and CMV retinitis occurred during the study period (Figure 11.3). It might have been assumed that the decreased incidence in AIDS defining illnesses observed might have immediately translated into a decline in expenditure on opportunistic infection. However, moving on from crude analysis of incidence to a detailed examination of the pharmacotherapy costs of four opportunistic infections illustrates that therapy costs are more reliant on disease prevalence than incidence (Figure 11.4).

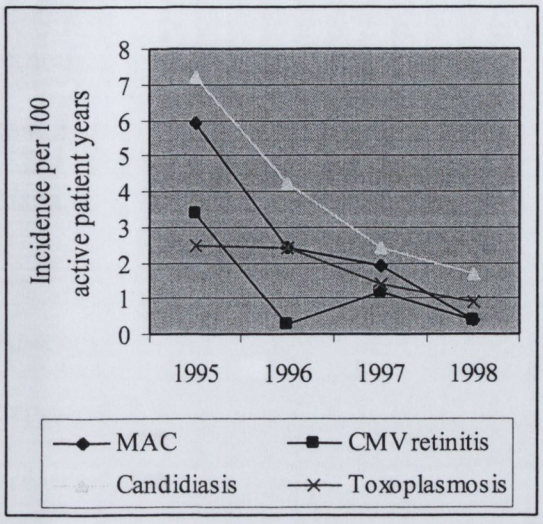


Figure 11.3 Annual incidence of MAC, toxoplasmosis, CMV retinitis and oesophageal candidiasis.

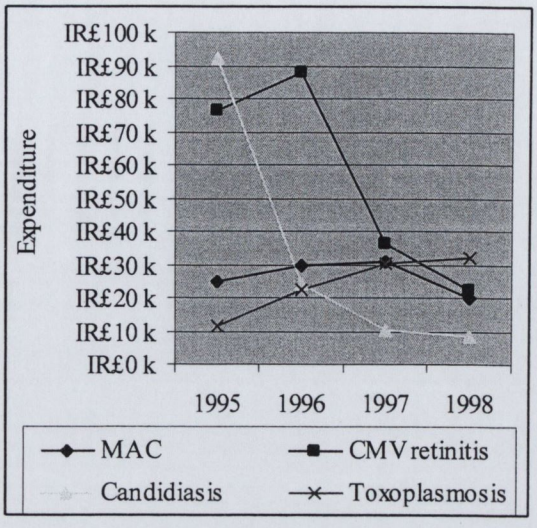


Figure 11.4 Annual outpatient expenditure on pharmacotherapy of MAC, toxoplasmosis, CMV retinitis and candidiasis.

Although improved morbidity subsequent to intensification of antiretroviral therapy resulted in a decreased incidence in MAC and toxoplasmosis, increased survival resulted in initially an accrual of the prevalent cohort, increased numbers of treatment days and therefore increased therapy costs. The ever changing nature of HIV therapeutics has resulted in a change in the policy of prescribing life long maintenance or secondary prophylaxis therapy for a number of opportunistic infections. Because of immune reconstitution in the era of HAART, patients who maintain a durable immunological and virological response to HAART may now have maintenance therapy discontinued. Therefore, in the case of MAC infection, the initial accrual of patients on MAC therapy was subsequently offset by the further decline in incidence and discontinuation of MAC maintenance therapy in patients who responded to HAART.

Expenditure on ethambutol was employed initially as an indicator of change in expenditure on MAC therapy. When expenditure on ethambutol unexpectedly increased subsequent to

the introduction of HAART and then decreased, it was decided to extend the analysis to examine expenditure on all of the agents used to treat this infection. In fact the pattern of expenditure on MAC therapy mirrored expenditure on ethambutol thereby validating the assumption that ethambutol is a useful indicator of expenditure on pharmacotherapy of this disease for the future (Figure 3.4).

Assessing the impact of HAART on toxoplasmosis revealed the limitations of measuring expenditure on anti-infective components of the treatment protocol alone. In fact, the greatest proportion of expenditure is attributed to adjunctive therapy with folinic acid. In addition a trend towards a requirement for higher doses of folinic acid was noted in patients maintained on toxoplasmosis therapy for durations unprecedented in the pre-HAART era. This change in the dose requirement for adjunctive therapy resulted in further increases in the overall cost of toxoplasmosis therapy.

Initial examination of outpatient expenditure on treatment of CMV retinitis reveals an increase in expenditure coincident with adoption of HAART in 1996 and then a decline in subsequent years. However unlike MAC and toxoplasmosis, increased expenditure was not a result of accrual of patients on therapy. Data on inpatient therapy of this disease was collected and in fact total expenditure on therapy of CMV retinitis declined coincident with the adoption of HAART as standard if care. The initial increase in outpatient expenditure may be explained by improved well being of the CMV treated cohort in the HAART era and the resultant shift to outpatient rather than inpatient therapy.

The impact of HAART on cost of treating candidiasis was the most immediate. Candidiasis is the only opportunistic infection examined in detail for which maintenance therapy is not routinely prescribed. For diseases treated acutely, expenditure on therapy mirrors incidence of disease. In the case of diseases for which chronic maintenance therapy is employed, expenditure is dependent on prevalence of disease. Mean cost per year per patient treated

for each of the three opportunistic infections associated with maintenance therapy i.e. MAC, toxoplasmosis and CMV retinitis increased over the study period. This may be explained by an increased number of days on therapy associated with increased survival and in the case of toxoplasmosis by an increased requirement for adjunctive therapy in patients receiving prolonged treatment courses. An awareness of the increase in cost per case treated in the HAART era would be important in predicting future expenditure for managing these three opportunistic infections.

Schrier et al examined the immune response to opportunistic antigens (MAC, toxoplasma, CMV and candida) in thirty HIV-infected patients with advanced disease before and after initiation of HAART [251]. At baseline, few responses to opportunistic antigens were noted. After HAART therapy, 60-70% of patients responded to CMV and candida antigens, 50% to MAC and only 20-30% to toxoplasma antigens. Of interest, on examination of the incidence rate of these four opportunistic infections in our cohort, the greatest decline in incidence subsequent to intensification of antiretroviral strategies was observed for CMV and candidiasis, followed by MAC and the smallest decline in incidence was observed for toxoplasmosis. In addition the greatest decline in expenditure on therapy was noted for CMV and candidiasis, a delayed decline was noted for therapy of MAC and expenditure on toxoplasmosis actually increased. Therefore, the recovery of response to opportunistic antigens *in vitro* appears to have been predictive of incidence rates and the pattern of expenditure of pharmacotherapy.

11.5 CDC classification of HIV disease

The 1993 CDC classification of HIV disease was in use at our centre throughout the study period [10]. Progression from stage A disease through stage B to stage C is unidirectional. In addition, each stage is sub-classified according to nadir CD4 cell count. In the pre-HAART era, Stage C or AIDS was considered to be associated with the greatest morbidity

and the largest resource implications in terms of inpatient care [135]. In addition, patients were not routinely prescribed antiretroviral therapy prior to stage C disease. Currently, patients in stage B disease are frequently prescribed antiretroviral therapy depending on CD4 cell count and plasma viral RNA as surrogate markers of disease progression. The proportion of our cohort in stage C disease increased over the study period from 47% in 1995 to 57% by study closure (Figure 11.5). This finding did not result in increased HIV-related morbidity, rather substantial decreases in incidence of opportunistic infection and in hospitalisation were observed. Patients diagnosed with opportunistic disease survive for longer periods of time than in the pre-HAART era. Therefore, it is no longer reasonable to assume that the current format of the CDC disease stage classification is a good predictor of HIV-related morbidity and resource consumption.

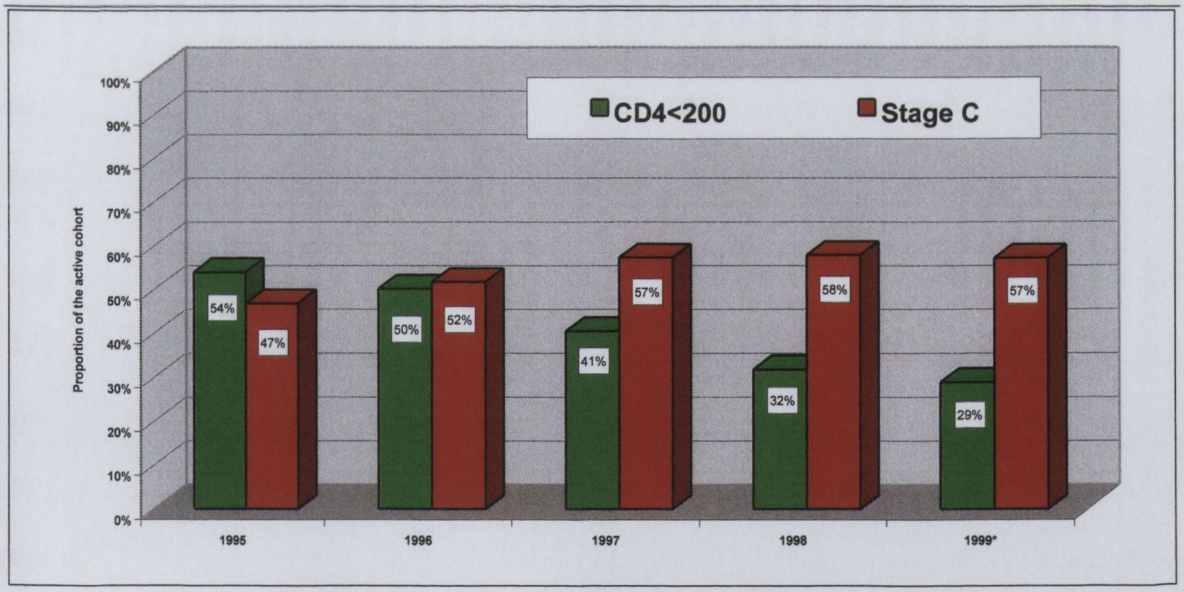


Figure 11.5 The proportion of the active cohort in Stage C disease and with a CD4 cell count < 200 x 10^6/L each year from 1995 to 1999*.

HIV-infected individuals with a CD4 cell count < 200 x 10^6/L are considered to be severely immunosuppressed and at increased risk of AIDS defining illnesses [55-57].

Therefore, a CD4 cell count below this threshold level is considered to be a Stage C defining condition according to the 1993 CDC classification of HIV disease [10]. In contrast to the observed increase in the proportion of the active cohort classified as Stage C disease, the proportion with a current CD4 count < 200 x 10^6/L declined from 54% in 1995 to 29% in 1999* (Figure 11.5) due to HAART induced immune reconstitution. The observation that the proportion of the cohort with a CD4 cell count < 200 x 10^6/L exceeds the proportion in Stage C in 1995 can be explained by the fact that CD4 cell counts were only available for 73.3% of active patient quartiles in that year.

The substantial improvement in the immunological profile of our cohort appears to be consistent with increased uptake of antiretroviral therapy and a decreased risk of opportunistic infection and hospitalisation. In addition, CD4 cell count at admission is inversely predictive of the cost of outpatient care. Therefore, the current classification of disease stage should become bi-directional by utilising the patient's current rather than nadir CD4 cell count. The resultant classification, which takes into consideration the degree of immune reconstitution, would be more relevant in clinical practice and estimation of resource consumption.

11.6 Diagnosis Related Group

Several studies have used DRG case-mix estimations of cost of inpatient admissions to populate pharmacoeconomic models of cost-effectiveness of new pharmacotherapeutic agents including HAART [252]. Based on the detailed study of cost of inpatient care, the DRG based estimation of cost of inpatient care grossly underestimates actual resource consumption. This finding may have grave implications in terms of underfunding the base hospital since in this country prospective budgets are in part determined by the casemix system. Reasons for the underestimation of actual costs by the casemix system may include inappropriate assignment of DRG codes to specific admissions, inadequacies in refinement

of costing data to calculate the monetary value of a baseline admission or inaccurate estimation of relative values attributable to specific DRGs. It is also possible that the DRG system is too cumbersome to keep pace with a therapeutic area such as HIV infection in which new and expensive interventions constantly and rapidly change the clinical presentation and therapeutic management of the disease. Pharmacoeconomic evaluations using assumptions based on DRG cost data are suitable for some less dynamic therapeutic areas but perhaps less relevant in others such as HIV infection. Interestingly since the major cost saving associated with HAART is reduced expenditure on hospitalisation, the cost-effectiveness of HAART in the Irish setting would be considerably less if the DRG estimation rather than the actual cost of inpatient care were used. However, the cost of inpatient care study indicates that the majority (58.5%) of the cost of inpatient care is attributed to ward costs, which are fixed for the most part. Therefore, it is valid to assume that expenditure on inpatient care is determined by the number of inpatient bed days.

From this study it is now evident that employing apparently plausible assumptions as a simplified means of estimating the impact of HAART on the pharmacoepidemiology and pharmacoeconomics of HAART would have been misleading. This study highlights the dangers inherent in simplistic approaches to what is a complex problem. This may be particularly characteristic of observational cohort analysis and pharmacoeconomic evaluations in HIV infection. Nevertheless, a number of erroneous assumptions relating to clinical outcomes and resource consumption in HIV disease have been refuted. In addition, a number of potential assumptions have been validated by this study and will prove useful for future work in this area.

11.7 Observational cohort databases

This thesis constitutes the first ever study of the pharmacoepidemiology and phramacoeconomics of HIV infection in Ireland. Conducting this study necessitated the

construction of a comprehensive observational cohort database spanning the pre-HAART and post-HAART eras as no such resource was previously in existence. This observational cohort database has been used to determine the history of HIV disease in a cohort with unrestricted access to HAART. The impact of the new treatment paradigms on the pharmacoepidemiology and the pharmacoeconomics of HIV and associated opportunistic disease has been determined. In addition this database has been used to determine the tolerability profile of the protease inhibitors in the Irish setting. In many other therapeutic areas the vast majority of information on efficacy with regard to clinical endpoints and on tolerability profiles is derived from randomised clinical trials. In the area of HIV disease management, observational databases have been greatly utilised to elucidate the natural history of untreated HIV infection and to characterise the effect of antiretroviral agents. Observational data supplement and complement clinical trial data particularly in this era of rapid drug development and increased reliance on changes in surrogate markers to license new therapies.

Information that may be derived from observational cohort studies includes:

- Long-term effectiveness of antiretroviral therapy in terms of disease progression, predictors of clinical outcome and the evolving history of HIV disease.
- Utilisation of drug therapy, physician prescribing patterns, patient compliance, development of resistance and durability of antiretroviral regimens. This information can be used in ecological studies, which examine overall survival and changes in outcome over time, looking at concurrent changes in access to therapy to see if there is an ecological relationship between exposure to a therapeutic agent and a change in outcome [253].
- Gender differences and differences amongst risk groups in utilisation and response to antiretroviral therapy.
- Efficacy of individual combination regimens at a time when the number of antiretrovirals is sufficiently large as to preclude comparative trials for all possible combinations.

- Natural history, prevalence and risk factors for opportunistic infections. [253]
- Long term safety data, surveillance of low incidence adverse effects and assessment of risk factors for toxicity.
- Data required for the economic assessment of any new intervention in a real world setting including uptake of the intervention, treatment related effects and subsequent changes in resource utilisation.
- Identification of patients for clinical trials.
- Data for AIDS surveillance and reporting.
- Data for administration and resource management of HIV services.
- Quantification of the cost of clinical care provision in HIV infection.

Observational databases have a number of advantages over randomised clinical trials. They allow long term follow-up of large numbers of patients. They are relatively inexpensive to maintain. The CDC's HIV Out-Patient Study (HOPS), which involves collection of data via an electronic charting system on 2,000 patients throughout the US, costs only approximately $200,000 per year [254]. If observational databases are integrated into routine patient care, they can enhance patient management by providing access to a clinical summary sheet detailing up to date patient information [255, 256]. Such clinical databases are usually accurate because physicians and other staff tend to regularly review the database during routine delivery of clinical care, thus allowing erroneous entries to be identified and corrected [256].

However there are some limitations to the use of observational databases. Many rely on data abstraction from primary case records. Serious clinical and adverse events are usually recorded diligently. However, inconsistent recording of less important clinical events or toxicity may occur [257]. In contrast to clinical trials, observational cohorts lack randomisation, which introduces the potential for bias, for example bias in treatment assignment [256]. A negative bias may be introduced if a therapy is only given to patients

who fail to respond to a less drastic treatment and who have a poor prognosis. Alternatively treatment might only be given to patients thought likely to respond, which would bias a treatment comparison in favour of the new intervention. Although data analysis can adjust for identifiable differences, it is impossible to be certain that such adjustments are adequate or that all the relevant characteristics of the patients have been documented [258]. Changes in diagnostic techniques and clinical definitions over time, missing data and use of different analytical approaches may be other confounding factors. Some bio statisticians have argued that observational studies are so inherently biased that only randomised controlled trials can be relied on to estimate treatment effects [259, 260]. However, two recent studies, which compared the results from observational studies and randomised controlled trials evaluating the same interventions, found that the results from observational studies did not systematically overestimate the magnitude of the effects of treatment as compared with those in randomised controlled trials [261, 262]. In addition randomised controlled trials utilise highly selected patient groups, which limits the generalisability of the results so that the optimal therapy for patients not meeting the selection criteria is unclear. Randomised controlled trials may prove too costly, difficult and time consuming to perform for every question of clinical interest [263]. Observational databases are useful adjuncts to randomised controlled trials to see whether efficacy under controlled conditions in clinical trials can translate into effective clinical management in routine practice. A recent investigation of antiretroviral therapy concluded that bias does exist in observational research but is not inevitable especially if the factors used for adjustment strongly predict the outcome [264].

11.8 Conclusion

This thesis includes the first cost of illness determination undertaken in Ireland and was carried out under the auspices of the National Centre for Pharmacoeconomics. The costing methodology employed in this study is an invaluable resource, as it will form the template

for future cost of illness studies in other therapeutic areas, which will be carried out at the Centre. Furthermore, data generated in this thesis can now be used for observational data comparative work, for example comparative analysis of antiretroviral strategies. It also provides the data necessary to populate decision models designed to assess the cost-effectiveness of different therapeutic strategies in the management of HIV-infected individuals, for example to assess the impact of therapeutic drug monitoring or phenotype resistance profiles. At a national level, these outcomes will undoubtedly help decision makers understand which treatments are not only effective but also represent substantial value in healthcare spending.

The pharmacoeconomic aspect of this thesis encompasses aspects of economics, epidemiology, bio statistics, clinical evaluation and decision theory. These pharmacoeconomic assessments generated interesting data on the associated costs and benefits of HAART. However, the more far-reaching application of this work is that applying simplistic pharmacoeconomic methodologies in HIV disease may lead to erroneous conclusions. It must be recognised that this type of health outcomes research, which applies pharmacoeconomic principles to assessing medical resource utilisation, is a relatively new discipline and poses methodological challenges especially in HIV disease. Although economists have used cost-benefit analysis for some time, in terms of its application to health policy, pharmacoeconomics is still in its relative infancy. As with most analytical techniques that are applied in new ways, it takes time to refine underlying methodologies and data sources [265]. It is important to develop rigorous methodologies to specifically address the pharmacoeconomics of HIV disease in order to provide a more evidentiary basis for decisions in HIV healthcare delivery throughout the world.

APPENDICES

APPENDIX I	**1993 revised classification for HIV infection and expanded case definition for AIDS in adolescents and adults [10].**
APPENDIX II	**Discharge diagnosis codes used to classify admissions of HIV-infected individuals.**
APPENDIX III	**Treatment guidelines for the management of oral and oesophageal candidiasis in HIV-infected patients at St. James's Hospital, Dublin.**
APPENDIX IV	**Assumptions used to calculate expenditure on virology tests for the active cohort.**
APPENDIX V	**Tolerability scale adapted from ACTG and MRC tolerability scales.**

APPENDIX I

1993 revised classification for HIV infection and expanded case definition for AIDS in adolescents and adults [10].

CD4 cell count	A	B	C
> 500 x 10^6/L (>29%)	A1	B1	C1
200 to 499 x 10^6/L (14% to 28%)	A2	B2	C2
< 200 x 10^6/L (<14%)	A3	B3	C3

Category A

Asymptomatic HIV infection
Persistent generalised lymphadenopathy
Acute retroviral syndrome

Category B

Bacillary angiomatosis
Oral or recurrent vulvovaginal candidiasis
Cervical dysplasia
Constitutional symptoms (fever of 38.5°C, diarrhoea > 1 month)
Oral hairy leukoplakia
Herpes zoster
Idiopathic thrombocytopaenia purpura (ITP)
Listeriosis
Pelvic inflammatory disease (PID)
Peripheral neuropathy

Category C (AIDS-defining conditions)

CD4 count <200 x 10^6/L
Candidiasis of oesophagus, pulmonary
[a]Cervical cancer
Coccidioidomycosis
Cryptococcosis, extrapulmonary
Cryptosporidiosis
Cytomegalovirus infection
Herpes simplex with oesophageal, pulmonary, or mucocutaneous involvement of >1 month
Histoplasmosis
HIV encephalopathy
Isosporiosis
Kaposi's sarcoma
Lymphoma
Mycobacterium avium complex or *Mycobacterium kansasii*
[a]*Mycobacterium tuberculosis*
Pneumocystis carinii pneumonia
[a]Pneumonia, recurrent with more than two episodes in 12 months
Progressive multifocal encephalopathy
Salmonellosis
Toxoplasmosis

[a]Added in the 1993 Centres for Disease Control revised case definition.

APPENDIX II

Discharge diagnosis codes used to classify admissions of HIV-infected individuals

ADR	Adverse drug reaction
BM	Bone marrow suppression including anaemia, neutropenia, thrombocytopaenia
CAN	Candidiasis
CMV	Cytomegalovirus infection
CRYPSPOR	Cryptosporidiosis
CRYPTOCOCC	Cryptococcal meningitis
DEM	HIV dementia or encephalopathy
HAEM	Management of haemorrhage in haemophiliacs
HEP	Hepatitis B or C related
HSV	Herpes simplex infection, for example encephalitis
HZV	Herpes Zoster infection
IDU	Complications of intravenous drug use, for example deep venous thrombosis
INF	Infection other than AIDS defining
KS	Kaposi's sarcoma
RTI	AIDS defining respiratory tract infection
MAC	*Mycobacterium avium* complex infection
MAL	Malignancy, for example CNS lymphoma, non-Hodgkin's lymphoma
OTH	HIV-related but not included in this list
NON	Non HIV-related, not already included in this list
PCP	*Pneumocystis carinii* pneumonia
PML	Progressive multifocal leucoencephalopathy
PRO	Procedure, for example gastroscopy
PSYC	Psychiatric admission
SKIN	Skin, for example psoriasis
TB	Tuberculosis
TOXO	Toxoplasmosis
WAS	HIV-related wasting

APPENDIX III

Treatment guidelines for the management of oral and oesophageal candidiasis in HIV-infected patients at St. James's Hospital, Dublin.

Treatment of oral and oesophageal candidiasis should follow a stepwise approach, starting at step 1 and progressing to each subsequent step only when the previous therapy has failed. In patients successfully treated with HAART, a lower dose of azole than previously required may be sufficient.

STEP 1: Patients should be encouraged to practice good oral hygiene. Patients with recurrent oral candidiasis should use chlorhexidine mouthwash regularly (10ml bd)

STEP 2: Consider nystatin (1ml four times daily) for the management of mild oral candidiasis with a CD4 cell count close to normal i.e. 500 x 106/L.

STEP 3: Fluconazole - start at the lowest effective dose and increase only if a satisfactory response is not obtained. Dose required depends on presenting symptoms (i.e. oropharyngeal or oesophageal) and history of azole use.

Oropharnyngeal: 50mg daily increasing to 100mg daily, if necessary for 5 - 7 days. Oesophageal: 100 - 200mg daily for 7 days. (Up to 400mg if required)

If the patient does not respond, resistance to fluconazole should be considered.

STEP 4: Itraconazole: Oropharyngeal: 100mg twice daily for 5 - 7 days
Oesophageal: 200mg twice daily for 7 days

STEP 5: Amphotericin 0.8mg /kg IV daily for 3 - 7 days increasing to a maximum dose of 1.5mg/kg/day if required.

For particularly resistant cases, flucytosine may be added (200mg/kg orally in four divided doses).

STEP 6: Amphotericin is nephrotoxic – therapy with the lipid encapsulated formulation of amphotericin *Abelcet*® at a dose of 2mg/kg may be substituted if:

1. serum creatinine rises to over twice the baseline value, or
2. serum creatinine >140ug/L, or
3. serum potassium cannot be maintained > 2.5mmol/L

If a patient is not responding to amphotericin 1 - 1.5mg/kg, *Abelcet*® 4mg/kg IV should be substituted.

APPENDIX IV

Assumptions used to calculate expenditure on virology tests for the active cohort.

Virology Test	Assumption
Plasma HIV RNA	5 per active patient per year (3 in 1996)
CMV antibody	4 per active patient per year
Toxoplasmosis antibody	4 per active patient per year
Hepatitis A antibody	1 per new attendee per year
Confirmatory HIV test	1 per new attendee per year
CMV buffy, DEAFF, PCR	1 each per CMV admission
HSV antibody, PCR	1 each per HSV encephalopathy admission

APPENDIX V

Tolerability scale adapted from ACTG and MRC tolerability scales

	GRADE I	GRADE II	GRADE III	GRADE IV
	Mild, transient, easily tolerated	Moderate discomfort, interrupts usual activity, requires medication	Severe interference with usual activity, discontinue drug	Life threatening, requires hospitalisation, incapacitating
Haemoglobin g/dl	8.0-9.4	7.0-7.9	6.5-6.9	<6.5
Absolute neutrophil count ($x10^9$/L)	1.0-1.5	0.75-0.999	0.5-0.749	<0.5
Platelets ($x10^9$/L)	75-99	50-74.9	20-49.9	<20
INR	1.0-1.25	>1.25-1.5	>1.5-3.0	>3.0
APTTR	>1.0-1.66	>1.66-2.33	>2.33-3.0	>3.0
Bilirubin (µmol/L)	>17-25.5	>25.5-42.5	>42.5-85	>85
Alkaline phosphatase (IU/L)	150-300	>300-600	>600-1200	>1200
Gamma glutamyl transferase (IU/L)	69-137	137-275	275-550	>550
Aspartate transferase (IU/L)	50-100	100-200	200-400	>400
Alanine transferase (IU/L)	44-88	88-176	176-350	>350
Hyponatraemia (mmol/L)	130-135	123-129	116-122	<116
Hypernatraemia (mmol/L)	146-150	151-157	158-165	>165
Hypokalaemia (mmol/L)	3.0-3.4	2.5-2.9 or K+ medication	2.0-2.4, intensive K+, hospitalisation	<2.0, arrhythmias, ileus, paresis
Hyperkalaemia (mmol/L)	5.5-6.0	6.1-6.5	6.6-7.0	>7.0, arrhythmias
Creatinine (µmol/L)	>125-187.5	>187.5-375	>375-750	>750, dialysis
Triglycerides (mmol/L)	>2.0-3.0	>3.0-4.0	>4.0-10.0	>10
Cholesterol (mmol/L)	>6.1-7.9	>7.9-9.76	>9.76-12.2	>12.2
Uric acid (µmol/L)	7.5-10.0	10.1-12.0	12.1-15.0	>15.0
Haematuria	Microscopic only	Gross, no clots	Gross+clots	Requires transfusion
Hypertension	Transient >20mmHg	Recurrent >20mmHg	Requires acute medication,	Requires hospitalisation
Neuro-psychiatric	N/A	N/A	Severe mood change, medication	Acute psychosis, hospitalisation
Neuromuscular paresis	Subjective weakness No objective signs	Mild objective signs/symptoms No decrease in function	Objective weakness Function limited	Paralysis
Paraesthesia	Mild discomfort, no medication	Mod discomfort, non-narcotic analgesia	Severe discomfort, responds to narcotics	Incapacitating, non-responsive to narcotics
Neuromotor	Decreased reflexes	Previously present reflex absent	2-3 previously present reflexes absent	Absence of > 3 previously present reflexes
Neuro-sensory	Decreased sensation, pinprick vibratory, hot/cold	Previously present sensation absent, 1 dermatome	2-3 previously present sensory, dermatomes absent	Absence of > 3 previously present reflexes, sensory dermatomes
Nausea	Mild, normal intake	Moderate, decreased intake>3/7	Severe, minimum intake>3/7	Hospitalisation

APPENDIX V (contd.) Tolerability scale adapted from ACTG and MRC tolerability scales

ITEM	GRADE I	GRADE II	GRADE III	GRADE IV
	Mild, transient, easily tolerated	Moderate discomfort, interrupts usual activity, requires medication	Severe interference with usual activity, discontinue drug	Life threatening, requires hospitalisation, incapacitating
Constipation	Mild	Moderate	Severe	Distention with vomiting
Abdominal pain	Mild, normal activity	Moderate, No medication	Moderate pain, medication	Severe pain, hospitalisation
Vomiting	2-3 per day, < 1 week	4-5 per day, > 1 week	Severe of all oral intake, IV therapy	Hypotensive shock, hospitalisation
Diarrhoea	3-4 per day, < 1 week	5-7 per day, > 1 week	>7 per day, bloody, IV therapy	Hypotensive shock, hospitalisation
Haemoglobin	8.0-9.4g/dl	7.0-7.9	6.5-6.9	<6.5
Dysphagia	Mild, no problem swallowing	Difficult swallowing, can eat	Unable to swallow solids	Unable to drink fluids
Headache	Mild, no medication	Moderate, non narcotic analgesia	Severe, initial response to narcotics	Intractable, requires repeated narcotics
Fatigue	Normal activity decreased <25%	Normal activity decreased 25-50%	Normal activity<50%, unable to work	
Allergic medication	Pruritus w/o rash	Localised urticaria	Generalised urticaria, angioedema	Anaphylaxis
Rash/Dermatitis	Erythema/pruritus	Diffuse maculopapular rash or dry desquamation	Vesiculation or ulceration, moist desquamation	Exfoliative dermatitis, SJS, mucous membrane involvement
Alopecia		Thinning of hair	Patchy loss of hair	Complete hair loss
Fever (°C)	37.7-38.5	38.6-39.5	39.6-40.5	>40.5

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Abbreviations:

↑	increased
↓	decreased
AMP	amprenavir
IDV	indinavir
NLF	nelfinavir
RTV	ritonavir
SQV	saquinavir

Notes:

*There have been case reports of this adverse reaction but incidence is unknown and the causal relationship between the protease inhibitor and this event may not have been established.

§Including some or all of the following: lipodystrophy (peripheral fat wasting), central adiposity, breast enlargement, gynecomastia, dorsocervical fat enlargement.

†Increased risk of bleeding has been reported occasionally in patients with haemophilia A or B receiving various protease inhibitors.

#The system of classification used is the FDA Pregnancy Category Scale (Federal Register 1980; 44: 37434–67).

This chart has been created to provide a summary of the adverse reactions to protease inhibitors in current use for the treatment of HIV disease. The data were compiled from a systematic review of the literature, in addition to the manufacturers' datasheets. It is not intended to be a comprehensive list of all of the adverse reactions that have been reported in clinical use. Priority is given to adverse reactions that are either: (i) frequently observed (ii) serious or (iii) considered clinically important in the opinion of the authors.

The tolerability of two or more protease inhibitors used in combination has not been addressed in this chart because of the relative scarcity of relevant data. Users are directed to look closely at the adverse drug reaction data for individual protease inhibitors, while bearing in mind that co-prescribing these agents is likely to result in increased serum concentrations and possibly enhanced toxicity.

Before prescribing any medication, please consult the full prescribing information of the product concerned.

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Adverse Reactions to Protease Inhibitors Summary Chart

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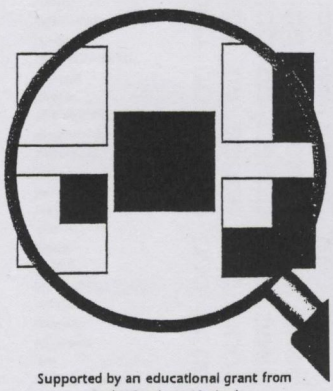

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Adverse reaction	AMP	IDV	NLF	RTV	SQV
ALLERGIC					
allergic reaction	☐	☐	◔	◔	◔
anaphylaxis	☐	◔	☐	◔	☐
angiooedema	☐	☐	☐	◔	☐
atopic rhinitis	☐	☐	☐	☐	◔
bronchospasm	☐	☐	◔	◔	☐
facial oedema	☐	☐	◔	◔	☐
Stevens–Johnson syndrome	◔	◔	☐	◔	◔
urticaria	☐	◔	◔	◔	◔
CARDIOVASCULAR					
hypotension	☐	☐	☐	◔	◔
syncope	☐	☐	☐	◔	◔
vasodilation	☐	☐	☐	◔	◔
CENTRAL NERVOUS SYSTEM					
anxiety	☐	☐	◔	◔	◑
asthenia/fatigue	◔	◑	◔	◑	◑
ataxia	☐	☐	☐	☐	◔
confusion	☐	☐	☐	◔	◔
depressed mood	◑	☐	◔	◔	◑
dizziness	☐	◑	◔	◑	◔
headache	◕[1]	◑	◔	◑	◑
hyperaesthesia	☐	◑	☐	◔	◔
insomnia	☐	◑	◔	◑	◑
paraesthesia, circumoral	■	☐	☐	◑	☐
paraesthesia, peripheral	◑	◑	◔	◑	◔
seizure	☐	☐	◔	◔	◔
somnolence	☐	◔	◔	◑	◔
suicidal ideation	☐	☐	◔	☐	◔
DERMATOLOGICAL					
alopecia	☐	◔	☐	☐	◔
dermatitis	☐	◔	◔	☐	◔
dermatitis, contact	☐	◔	☐	◔	☐
dry skin	☐	◕	☐	◔	☐
eczema	☐	☐	☐	◔	◔
erythema	◔	☐	☐	☐	◔
folliculitis	☐	◔	◔	◔	◔
paronychia/ingrown toenails	☐	◔[2]	☐	☐	☐

Adverse reaction	AMP	IDV	NLF	RTV	SQV
DERMATOLOGICAL (cont)					
photosensitivity	☐	☐	☐	◔	◔
pigment changes	☐	◔	☐	☐	◔
pruritus	☐	◑	◔	◔	◔
psoriasis	☐	☐	☐	◔	◔
rash	◕	◕	◑	◔	◑
rash, maculopapular	◕	☐	◔	◔	◔
rash, vesiculobullous	☐	☐	☐	◔	☐
ELECTROLYTE DISTURBANCE					
calcium ↓	☐	☐	☐	◔	◔
calcium ↑	☐	☐	☐	☐	◔
potassium ↓	☐	☐	☐	◔	◔
potassium ↑	☐	☐	☐	◔	◔
sodium ↓	☐	☐	☐	◔	◔
sodium ↑	☐	☐	☐	☐	◔
ENDOCRINE/METABOLIC					
creatinine phosphokinase ↑	☐	☐	◑	◑	◑
diabetic ketoacidosis	◔	◔	◔	◔	◔
diabetes mellitus, new-onset	◔	◔	◔	◔	◔
fat redistribution syndrome[4]	■	■	◔	■	☐
gout	☐	☐	☐	◔	☐
hypercholesterolaemia	◔	■[3]	■[3]	■[3]	◑[4]
hyperglycaemia	◑	◕[5]	◑[5]	◔	◑[5]
hypertryglyceridaemia	◕	■[6]	■[6]	■[7]	◑[4]
hyperuricaemia	☐	☐	◔	◑	☐
hypoglycaemia	☐	☐	◔	☐	◔
hypothyroidism	☐	☐	☐	◔	◔
lactate dehydrogenase ↑	☐	☐	◔	◔	☐
EAR, NOSE AND THROAT					
cerumen ↑	☐	☐	☐	◔	☐
earache	☐	☐	☐	◔	◔
ear pressure	☐	☐	☐	☐	◔
epistaxis	☐	☐	☐	◔	◔
hearing impairment	☐	☐	☐	◔	◔
pharyngitis	☐	◔	◔	◑	◔
rhinitis	☐	☐	◔	◔	☐
sinusitis	☐	◔	◔	☐	◔

Adverse reaction	AMP	IDV	NLF	RTV	SQV
EAR, NOSE AND THROAT (cont)					
throat irritation	☐	☐	☐	◑	☐
tinnitus	☐	☐	☐	◔	◔
GENITOURINARY/RENAL					
haematuria	☐	◔	☐	◔	☐
hydronephrosis	☐	◔	☐	☐	☐
impotence	☐	☐	◔	◔	◔
nephrolithiasis	☐	◑	◔	◔	◔
proteinuria	☐	◔	◔	☐	☐
renal insufficiency	☐	◔	☐	◔[8]	◔
GASTROINTESTINAL					
abdominal distension	☐	◔	◔	◔	◔
abdominal pain	◔[1]	◑	◑	◑	◑
acid regurgitation	☐	◔	☐	☐	☐
amylase ↑	☐	◑	◔	◔	◔
anorexia	☐	◔	◔	◔	◔
cheilitis	☐	☐	☐	◔	◔
constipation	☐	☐	☐	☐	◔
diarrohea	■	■	■	◕	◕
dry mouth	☐	◔	☐	◔	◔
dyspepsia	☐	◕	◔	◑	◑
flatulence	◔[1]	◑	◑	◔	◑
hailtosis	☐	◔	☐	☐	☐
mouth ulceration	☐	☐	◔	◔	◔
nausea	■	◕	◑	■	◕
pancreatitis	☐	☐	◔	◔	◔
taste perversion	◑	◑	☐	◕	◑
vomiting	◕	◑	◔	◕	◑
HAEMATOLOGICAL					
anaemia	☐	◔	◔	◔	◔
anaemia, acute haemolytic	◔	◔	☐	☐	◔
bleeding[1], risk of ↑	◔	◔	◔	◔	◔
leucopenia	☐	☐	☐	◔	☐
lymphocytopenia	☐	☐	◔	☐	☐
lymphocytosis	☐	☐	☐	◔	☐
neutropenia	☐	◑	◑	◔	◔
pancytopenia	☐	☐	☐	☐	◔

Adverse reaction	AMP	IDV	NLF	RTV	SQV
HAEMATOLOGICAL (cont)					
prothrombin time ↑	☐	☐	☐	◔	☐
thrombocytopenia	☐	◔	☐	◔	☐
HEPATIC					
alanine aminotransferase ↑	☐	◑	◔	◑	☐
alkaline phosphatase ↑	☐	☐	◔	◔	☐
aspartate aminotransferase ↑	☐	◑	◔	◑	☐
billirubin ↑	☐	◕	☐	◔	☐
γ-glutamyltransferase ↑	☐	☐	◔	◑	☐
hepatitis	☐	◔	◔	◔	☐
hepatomegaly	☐	☐	☐	◔	☐
jaundice	☐	◔	☐	◔	☐
MUSCULOKELETAL					
arthralgia	☐	◔	◔	◔	☐
myalgia	☐	◔	◔	◔	☐
OPHTHALMOLOGICAL					
abnormal vision	☐	◔	☐	◔	☐
conjunctivitis	☐	☐	◔	☐	☐
iritis, acute	☐	☐	◔	◔	☐
photophobia	☐	☐	☐	◔	☐
uveitis	☐	◔	☐	◔	☐
RESPIRATORY					
asthma	☐	☐	☐	◔	◔
cough ↑	☐	◔	☐	◔	◔
hypoventilation	☐	☐	☐	◔	☐
SYSTEMIC					
body odour	☐	◔	☐	☐	☐
dehydration	☐	☐	◔	◔	◔
fever	☐	◔	◔	◔	◔
flu-like symptoms	☐	◔	☐	◔	☐
TERATOGENIC#	CAT C	CAT C	CAT B	CAT B	CAT B

Key to incidence scale:

☐ Not reported
◔ Rare (<2%)
◑ 2–10%
◕ 10–20%
■ >20%

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he Irish National Centre of Pharmacoeconomics: s Rationale and Role

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roduction

The Irish National Centre of Pharmacoeconomics was established in 1998 with financial support from the Department of Health and ldren. Its aim is to promote expertise in Ireland for the ancement of the discipline of pharmacoeconomics through ctice, research, and education (Figure 1). The Centre's main vity will be the economic evaluation of pharmaceutical products, the development of cost-effective prescribing. The latter will us on new and existing drugs funded by the General Medical vices (GMS) payments board, along with routine prescribing by eral practitioners. The Centre will also be involved in research into h cost areas (for example, lipid-lowering drugs) together with a tribution to the undergraduate pharmacology curriculum.

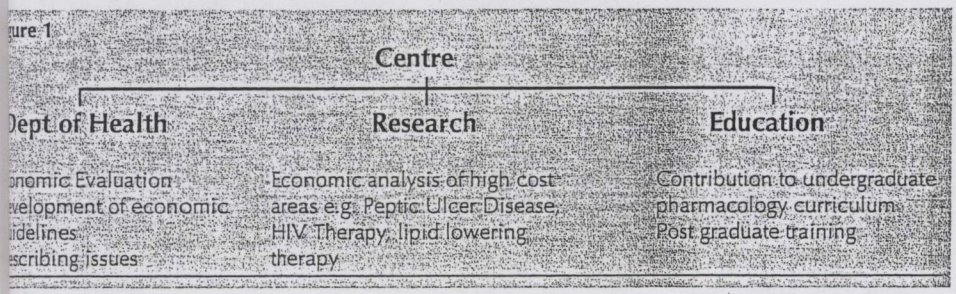

Figure 1

tionale

increasing age of developed countries' populations, the rapid ansion of the absolute number of drug therapies, and the increasing numbers of drugs taken in combination, have increased health budgets world-wide; health expenditure is now approximately 8% of the world's total gross national product [Table 1][1,2]. This growth has brought about the application of economics to health budgets by governments (especially in relation to expenditure on drugs) in an effort to balance spending with taxation income.

Economics can be seen as a mechanistic approach to sensitive issues which may be difficult to explain to those outside the medical profession. However, clarification of the resource implications of different choices (between treatments, drugs, or surgical procedures) makes better decision making possible. As resources are limited, timely and relevant information about costs and outcomes helps to move the health system towards the maximum health impact of a given budget. Economics is not a substitute for sound clinical judgement but it can pose serious questions about priorities.

The size of the prioritisation problem is demonstrated by the volume of spending on drugs. In 1998, total government estimated expenditure was £12.871 billion, of which the Department of Health and Children budget was estimated to be £2.823 billion (22% of the total [Table 2])[3]. This is an increase of 10% compared to estimated expenditure in 1997 and is the largest percentage of government funds allocated to any public service. Of the other 43 separate supply services, only the Department for Social Security and Family Affairs approaches this size, at £2.793 billion.

In 1997, the GMS payments board spent approximately £388 million which was approximately 15% of the total estimated expenditure for the Department of Health and Children for that year. The board is responsible for drug payments to the general practitioners, pharmacists and dentists taking part in government funded health service schemes. There are 11 schemes controlled by the GMS payments board, but the main expenditure is the General Medical Services scheme itself, which used approximately 73% of the total GMS income in 1997[4,5].

35% of the population are eligible for the GMS scheme, which offers a medical card to provide free general practitioner services and drugs and appliances supplied under the scheme. Those eligible are "persons who are unable without undue hardship to arrange general practitioner medical and surgical services for themselves and their dependants"[6]. In 1997, more than 83% of eligible GMS persons availed of the scheme and in excess of 23.5 million prescription items were paid for by the board; this was an increase of almost 1.5 million since the previous year[4]. However, it is not widely realised that substantial

ble 1: % Share of Gross Domestic Product in Health Care in Selected European Countries, in selected years.

untry	1960	1975	1989	1995
land	4.0	7.8	6.5	6.1
rmany*	4.7	7.8	8.2	10.3
lgium	3.4	5.8	7.2	8.0
nmark	3.6	6.5	6.3	6.4
nce	4.2	6.8	8.7	10.0
y	3.9	5.8	7.6	7.9
therlands	3.9	7.7	8.3	8.8
in	2.3	5.1	6.3	7.6
eden	4.7	8.0	8.8	7.1
ited Kingdom	3.9	5.5	5.8	6 9
erage	3.8	6.6	7.5	7.9

hese figure are for West Germany pre 1989 and united Germany n 1995

e 2: Republic of Ireland Supply of Government Services for 1998

ice	Estimated Cost (£IR billions)	Percentage
ronment and l Government	1.015	8 %
rity	0.774	6%
cation	2.404	19%
al, Community and ily Affairs	2.794	22%
lth and Children	2.823	22%
ers	3.061	23%

ditures by the GMS are to the general public, not to means- patients; announcing the recent (March 1999) creation of the Payments scheme (from the Drugs Cost Subsidisation Scheme Drug Refund Scheme), the Minister said: "The new Drugs ents Scheme is for everyone.... In effect, where expenditure by a y exceeds £42 per month, the balance will be met by the State." rtment press release, 1/12/98).

neral, expenditure on medicines in Ireland under the Community nes (GMS, Drugs Payment Scheme, Long Term Illness scheme , etc.) has been increasing significantly. Using data from the , LTI and the High Tech Drug scheme (latter introduced in Nov. , which are among the most costly community schemes ned by the GMS payments board, it can be shown that the dient cost of medications has increased from £166 million in to £258 million in 1997 (Table 3). Combined with this increasing diture on drugs, there is also a perception that drug budgets in al may not currently be used to the best advantage, and that it e possible for savings to be made without detriment to patients.

e 3: Expenditure on medicines in Ireland 1993 - 1997 (includes expenditure of medicines from the GMS, DCSS, LTI and High Tech Drug schemes)

Year	Cost £IR Millions
1993	166
1994	179
1995	198
1996	215
1997	258

ationale for the National Centre of Pharmacoeconomics is the vement of the maximum health impact of drugs, per unit of diture, through the evaluation, in cost-effectiveness terms, of ng products, and of products which pharmaceutical companies forward for adoption by the GMS Payments Board[7,8]. Because e economic pressures referred to above, the demand for macoeconomic data is increasing world-wide. In the next three there is an expectation that the number of pharmacoeconomic rs to reimbursement authorities will globally increase by 87%, e number of submissions to pricing authorities by 74%. To help modate this, there are pharmacoeconomic centres or the lent in many countries (including Canada, the US, France, the nd Australia) and pharmacoeconomic departments are growing y in pharmaceutical companies. In 1990, the average company Full Time Equivalent) staff in a pharmacoeconomic department but this had risen to 24 in 1998. Figures for 1998 also show that erage annual budget of such a department (in a pharmaceutical any) was greater than one million US dollars for approximately of cases, and greater than six million dollars in approximately

The Role of the Centre

There are four main aspects, liaison with the National Medicines Information Centre, research, the pharmaceutical industry, and educational activities.

Liaison with the National Medicines Information Centre (NMIC)

The NMIC is responsible for providing independent, unbiased information to all healthcare professionals in Ireland; the main users are doctors and pharmacists who enquire for information on new products, choice of therapy, etc. Since cost-effective prescribing uses both evidence-based medicine and pharmacoeconomics, the Centre of Pharmacoeconomics works closely with the NMIC; both centres operate from the same location in St. James's Hospital, and are funded by the Department of Health and Children.

The NMIC also provides information in the form of therapeutic bulletins. These publications, which are distributed to all doctors and pharmacists, highlight new drug developments and, amongst other things, give details on changes in the therapeutic management of a disease condition. More recent bulletins have also incorporated a brief section on the pharmacoeconomics of a given drug or therapeutic area; this focus will continue in the future.

Research

Projects which are currently in progress include:

a) The cost-effectiveness of combination antiretroviral therapy for HIV

b) The evaluation of treatments for Alzheimer's Disease

c) The cost-effectiveness of treatments for hyperlipidemia

d) The modelling of prescribing for Chronic Heart Failure

e) The review of prescription patterns for Peptic Ulcer disease

f) The use of different measures of health outcome, as bases for resource allocation.

g) The average costing of an MI in the Irish setting.

The centre also aims to focus on other high cost areas such as depression and asthma.

The Pharmaceutical Industry

It is not widely known that Ireland is a substantial producer of pharmaceutical products, exporting the largest quantity, per head of population, of any country in the European Union. Ireland also has the third largest pharmaceutical trade surplus, of all the EU countries[10]. The long-term success of this important sector depends on the rigorous application of scientific methods to the economics, as well as to the pharmaceutical development, of drug entities.

The Centre evaluates drugs in terms of the evidence for their cost-effectiveness, when required to do so by the Department of Health and Children. Often, the case made for a drug, and its application to the Irish context, may be capable of more than one interpretation and the evidence from other countries will have to be interpreted for the Irish context. To facilitate such evaluations, the Centre has developed Pharmacoeconomic Guidelines, which are currently under discussion between the Centre, the Department of Health and Children, and the Irish Pharmaceutical and Healthcare Association. The aim of these guidelines is to ensure enough consistency in pharmacoeconomic submissions to allow the results from different studies to be compared in a meaningful way.

Educational Activities

The centre's educational activities include a contribution to the undergraduate clinical pharmacology curriculum in Trinity College, Dublin, and to post-graduate training in pharmacology. It will also be acting as a tutorial centre for the Health Economics correspondence course organised by the Health Economics Research unit at Aberdeen University, commencing in September of this year.

usion

nics is the language of scarcity and choice. It gives an ess of the resource dimension of the difficult decisions which reasingly necessary in a health service faced with unlimited d for its services, but possessed of limited resources to meet demands. The National Centre of Pharmacoeconomics is tted to the strategic development of cost-effective prescribing, e look forward to co-operating with colleagues in medicine, ment, and the pharmaceutical industry, to maximise the impact th of the drug budget over the long term.

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PRESENTATIONS ARISING FROM THIS THESIS:

A comparative review of adverse drug reactions to protease inhibitors in an Irish clinic setting.

M Ryan, C Merry, P Harrington, A Heerey, S Clarke, M Barry, F Mulcahy.

STIs and the millennium: past, present and future. A joint meeting of the American Sexually Transmitted Diseases Association & Medical Society for the Study of Venereal Disease, Baltimore, Maryland. May 2000. Abstract 260.

Identifying the changing needs of an Irish HIV-infected cohort from 1995 to 1999*.

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STIs and the millennium: past, present and future. A joint meeting of the American Sexually Transmitted Diseases Association & Medical Society for the Study of Venereal Disease, Baltimore, Maryland. May 2000. Abstract 261.

Incidence and cost of treating opportunistic infection in an HIV-infected cohort in the era of highly active antiretroviral therapy.

M Ryan, C Merry, P Harrington, M Barry, F Mulcahy.

National Scientific Medical Meeting, Dublin. April 2000. Abstract 147.

A prospective evaluation of adverse drug reactions to protease inhibitors in an Irish clinic setting.

M Ryan, C Merry, P Harrington, A Heerey, F Mulcahy, M Barry.

National Scientific Medical Meeting, Dublin. April 2000. Abstract 167.

Changes in the demographics of new attendees at an Irish HIV clinic from 1995 to 1999*.

M Ryan, S Clarke. C Merry, P Harrington, F Mulcahy, M Barry.

National Scientific Medical Meeting, Dublin. April 2000. Abstract 101.

Changing mortality and hospitalisation in an Irish HIV-infected cohort.

M Ryan, C Merry, A Kelly, A Heerey, B McGowan, C Ryan ,F Mulcahy, M Barry.

National Scientific Medical Meeting, Dublin. April 2000. Abstract 148

Changing pharmacoepidemiology and cost of treating three opportunistic infections in an Irish HIV-infected cohort

M Ryan, C Merry, A Kelly, F Mulcahy, M Barry.

Seventh European Conference on Clinical Aspects and Treatment of HIV infection, Lisbon. October 1999. Abstract 883.

Changing mortality and hospitalisation in an Irish HIV-infected cohort.

M Ryan, C Merry, A Kelly, A Heerey, B McGowan, C Ryan, F Mulcahy, M Barry.

Seventh European Conference on Clinical Aspects and Treatment of HIV infection, Lisbon. October 1999. Abstract 478.

The impact of triple antiretroviral therapy on opportunistic infection in an Irish HIV-infected cohort.

M Ryan, C Merry, K Sabra, P Harrington, F Mulcahy, M Barry.

Oral presentation at the 58th Pharmacy World Congress, Lisbon. September 1999. Abstract HPS-O-004.

The impact of triple antiretroviral therapy on treatment of MAC infection.

M Ryan, C Merry, M Barry, P Harrington, F Mulcahy.

Fifth Annual meeting of the British HIV Association, Cambridge. March 1999.

The impact of triple combination therapy on MAC infection.

M Ryan, C Merry, M Barry, P Harrington, F Mulcahy.

National Scientific Medical Meeting, Dublin. April 1999. Abstract 147.

The effects of the introduction of protease inhibitors on the frequency and severity of candida infection in patients with HIV.

P Ormond, M Ryan, C McCreery, F Mulcahy.

Seventy-fifth Spring meeting of the Medical Society for the Study of Venereal Disease. Oxford. April 1999.

Tolerability of protease inhibitors.

M Ryan, L Byrne, C Merry, M Barry, F Mulcahy.

Second Conference of the European Association of Hospital Pharmacy, Porto. March 1997.

The impact of triple antiretroviral therapy on opportunistic infection in an Irish HIV-infected cohort.

M Ryan, C Merry, K Sabra, P Harrington, F Mulcahy, M Barry.

Oral presentation at the 58th Pharmacy World Congress, Lisbon. September 1999. Abstract HPS-O-004.

With the availability of the protease inhibitors in 1996, triple antiretroviral therapy (TAT) replaced dual therapy as standard of care for the management of HIV infection. A significant decrease in the rate of opportunistic infections (OIs) following widespread use of TAT has been reported. Using drug expenditure reports for the HIV OPD pharmacy the change in epidemiology of a number of OIs in our cohort in pre and post TAT eras (1995, 1998) has been examined
Initial results for *Mycobacterium avium* complex(MAC) and Toxoplasmosis are available. Results for Oral and Oesophageal Candidiasis and Cytomegalovirus Retinitis will be presented also.

Results

	1995	**1998**
Drug Expenditure on MAC Tx.	31,721.71 EURO	25,425.87 EURO
No. of patients on MAC Tx.	30	15
Drug Expenditure on Toxoplasmosis	15,002.46 EURO	40,845.25 EURO
No. of patients on Toxoplasmosis Tx	14	14

Annual expenditure on MAC has decreased while expenditure on Toxoplasmosis has increased. The impact of TAT on OIs is therefore more complex than initially apparent and needs further evaluation.

Changing mortality and hospitalisation in an Irish HIV-infected cohort.

M Ryan, C Merry, A Kelly, A Heerey, B McGowan, C Ryan, F Mulcahy, M Barry.

Seventh European Conference on Clinical Aspects and Treatment of HIV infection, Lisbon. October 1999. Abstract 478.

Backround of study: 777 patients attended St James's Hospital, Dublin between 1/95 and 6/99, representing the largest cohort of HIV-infected individuals in Ireland. Highly Active Anti-retroviral therapy(HAART) was adopted as standard of care for the management of HIV-infection in our centre from March 1996 coincident with the availability of the protease inhibitors.
Objective: To examine mortality and hospitalisation rate in the era of HAART in an Irish HIV-infected cohort.
Design: Trends in antiretroviral usage, mortality and hospitalisation rate in all patients who attended our service from 1/95 onwards were examined. A database including patient demographics, antiretroviral use, hospitalisation rate and mortality was constructed. Data was stratified according to calendar quartile .
Results: Data to the end of 1998 for approximately 75% of the cohort has been analysed to date. Prescribing of HAART increased from 17.4% of the cohort at the end of the 2nd quartile in 1996 (Q2-96) to 52.7% at the end of 1998. Annual mortality fell from 12.5 per 100 person years (100 P-Ys) in 1995 to 2.82 per 100 P-Ys in 1998. Hospitalisation rate and the number of in-patient days decreased from 70.6 admissions and 635.3 days per 100 P-Ys in 1995 to 49.2 admissions and 449.9 days per 100 P-Ys in 1998 respectively.
Conclusion: Dramatic reductions in mortality and hospitalisation from 1995 to 1998 coincided with the adoption of HAART as standard of care. Data for the entire cohort to the 2nd quartile of 1999 will be presented.

Changing pharmacoepidemiology and cost of treating three opportunistic infections in an Irish HIV-infected cohort

M Ryan, C Merry, A Kelly, F Mulcahy, M Barry.

Seventh European Conference on Clinical Aspects and Treatment of HIV infection, Lisbon. October 1999. Abstract 883.

Backround of study: 800 patients attend our centre representing the largest cohort of HIV-infected individuals in Ireland. HAART was adopted as standard of care for the management of HIV-infection in our centre from March 1996 coincident with the availability of the protease inhibitors. Consequently out-patient drug expenditure including antiretroviral therapy (ART)and management of opportunistic infections (OIs) increased from IR£500,000 to IR£2,000,000.It has been postulated that increased ART costs would be offset by decreased cost of managing OIs.
Objective: To examine pharmacoepidemiology and cost of treating *Mycobacterium avium* complex (MAC), Toxoplasmosis (Toxo) and Recurrent Oral & Oesophageal Candidiasis (ROC) in the era of HAART in an Irish HIV-infected cohort.
Design: Drug usage reports from the satellite pharmacy in the HIV out-patient clinic were used to quantify annual drug usage and expenditure on the treatment of MAC, Toxo and ROC from 1995 to 1998. Incidence of opportunistic infection and antiretroviral usage were abstracted from a recently constructed cohort data base. Trends in HAART usage in the cohort and trends in new diagnoses, numbers on treatment and costs for each opportunistic infection were determined.
Results: Prescribing of HAART increased from 17.4% of the cohort at the end of the 2nd quartile in 1996 to 52.7% at the end of 1998.
ROC: The number of patients who received therapy for ROC decreased from 32.39/100 PYs in 1995 to 19.76/100 PYs in 1998. Expenditure on ROC therapy decreased from IR22,127.25 in 1995 to IR8424.22 in 1998.
MAC: The number of new diagnoses of MAC fell from 5.4 per 100 person years (/100 PYs) in 1995 to 0.6/100 PYs in 1998. The total number of patients on MAC therapy decreased from 7.36/100 PYs in 1995 to 3.19/100 PYs in 1998.Expenditure on MAC therapy decreased from IR24,982.88 in 1995 to IR20,024.50 in 1998.
Toxo: The number of new diagnoses of Toxo fell from 2.21/100 PYs in 1995 to 0.6/100 PYs in 1998. The total number on therapy remained constant (3.19/100 PYs in 1995, 2.99/100 PYs in 1998). However expenditure on Toxo therapy increased from IR11,815.40 to IR32,168.25 over the same time period.
Conclusion: Dramatic decreases in numbers treated for ROC, MAC and Toxo occurred subsequent to the adoption of HAART as standard of care. Expenditure on ROC therapy decreased to a greater extent than the number of patients on therapy due to a decreased requirement for the higher dose salvage regimens. New diagnoses of MAC and Toxo decreased significantly. Decreased attrition rate of the cohort associated with more potent antiretroviral efficacy has resulted in a smaller reduction in the number of patients on MAC maintenance and no decrease in the numbers treated for Toxo. Expenditure on MAC therapy decreased over the study period. However expenditure on Toxo therapy increased almost three fold due to increased number of patient treatment days associated with increased survival. Total drug acquisition costs for the three OIs studied actually increased from 1995 to 1998. The implication that the increase in ART costs associated with HAART might be offset by decreased costs of OI drug treatment requires further analysis.

Incidence and cost of treating opportunistic infection in an HIV-infected cohort in the era of highly active antiretroviral therapy.

M Ryan, C Merry, P Harrington, F Mulcahy, M Barry.

National Scientific Medical Meeting, Dublin. April 2000. Abstract 147.

With the availability of the protease inhibitors in 1996, Highly Active Anti-Retroviral Therapy (HAART) replaced dual therapy as standard of care for the management of HIV infection. A significant decrease in the rate of opportunistic infections (OIs) following widespread use of HAART has been reported. Using drug expenditure reports for the HIV OPD pharmacy the change in epidemiology and cost of treating *Mycobacterium avium* complex(MAC), Toxoplasmosis (Toxo) and Recurrent Oral and Oesophageal Candidiasis (ROC) in our cohort in the pre and post HAART eras (1995, 1998) was examined.

Results

	1995	**1998**
No. of new diagnoses of MAC	5.4/100 PY	0.6/100PY
No. of patients on MAC Rx.	7.36/100 PY	3.19/100PY
Drug expenditure on MAC Rx.	IR£24,982.88	IR£20,024.50
No. of new diagnoses of Toxo	2.21/100 PY	0.6/100 PY
No. of patients on Toxo Rx	3.19/100PY	2.99/100 PY
Drug expenditure on Toxo Rx	IR£11,815.40	IR£32,168.35
No of patients treated for ROC	32.39/100 PY	19.76/100PY
Drug expenditure on ROC Rx	IR£22,127.25	IR£8,424.22

The number of new diagnoses of each OI decreased significantly. Annual expenditure on MAC and ROC decreased while expenditure on Toxo increased. The economic impact of HAART on OIs is complicated by decreased attrition rate of the cohort associated with increased survival.

Changes in the demographics of new attendees at an Irish HIV clinic from 1995 to 1999*.

M Ryan, S Clarke. C Merry, P Harrington, F Mulcahy, M Barry.

National Scientific Medical Meeting, Dublin. April 2000. Abstract 101.

Changes in the Demographics of New Attendees at an Irish HIV clinic from 1995 to 1999*.
M. Ryan*, S. Clarke, C. Merry, P. Harrington, M. Barry, F. Mulcahy.
St. James's Hospital, James's Street, Dublin 8, Ireland.

Introduction: St. James's Hospital, Dublin provides in-patient and out-patient care for the largest HIV-infected cohort in Ireland. 777 patients attended between 1/95 and 6/99. Demographic trends in new attendees were examined in order that the service could adapt to the changing needs of the cohort.

Method: A comprehensive database detailing patient demographics, antiretroviral history, disease indicators(viral RNA, CD4, AIDS defining illnesses) and hospital admissions has recently been constructed. Data was abstracted from patient charts, pharmacy records, and laboratory records. Database analysis revealed the following demographic trends.

Results: The results are summarised in the following graphs.

Discussion: Reasons for these changes in demographic characteristics of new attendees may include:

- a change in policy by the National Haemophilia Centre to refer haemophilacs to our clinic for HIV care
- increased HIV testing of young IDUs by the Drug Treatment Service subsequent to centralisation of methadone maintenance in the latter half of 1998
- Ireland's recently increasing refugee population
- adoption of a national ante-natal HIV screening program in 1998

Conclusion: This study illustrates changing demographic patterns amongst new attendees and facilitates adaptation of the healthcare and support services provided by our clinic to the changing needs of our patient cohort. In particular, the needs of our increasing numbers of women, young IDUs and non-nationals for whom English is not a first language are being addressed.

1999*-data to 6/99 only

A comparative review of adverse drug reactions to protease inhibitors in an Irish clinic setting.

M Ryan, C Merry, P Harrington, A Heerey, S Clarke, M Barry, F Mulcahy.

STIs and the millennium: past, present and future. A joint meeting of the American Sexually Transmitted Diseases Association & Medical Society for the Study of Venereal Disease, Baltimore, Maryland. May 2000. Abstract 260.

Highly Active Anti-Retroviral Therapy has been the standard of care for the management of HIV infection in Ireland since the introduction of protease inhibitors (PIs) in March 1996. All adverse drug reactions(ADRs) were recorded prospectively facilitating a comparative evaluation of the tolerability of the protease inhibitors in the clinical setting.
Method: We recorded date of initiation of the PI, date of and reason for discontinuation and concomitant drug therapy. ADRs were graded according to an intensity scale (I - IV, I if mild, IV if severe) and relationship to the PI component of the combination (A - C, A if unlikely, C if very likely).
Results: By June 1999, 351 patients had been prescribed protease inhibitors as part of combination antiretroviral therapy representing 625 patient-PI exposures. Patient drug exposures including dual PI therapy were excluded from this analysis. The most commonly prescribed PIs were saquinavir$_{hgc}$ (SQV) included in 199 exposures , Ritonavir(RTV) in 67, indinavir(IDV) in 145 and nelfinavir(NFV) in 204. There were 2182 ADRs to these PIs occurring in 320 patients. Of these ADRs, 1970 were graded C i.e. considered very likely to be due to the PI in the combination. Grading these C ADRs according to intensity revealed 945 (I), 704 (II), 283 (III), 38 (IV). Diarrhea was the most commonly noted ADR with an overall incidence of 28.3 [ranging from 11.7% with IDV to 50.7% with RTV]. Nausea occurred in 23% [ranging from 10.3% with NFV to64.2% with RTV]. Drug specific ADRs included nephrolithiasis with an incidence of 20.7% in association with IDV, hyperbilirubinaemia with an incidence of 51.7% also with IDV and perioral paraesthesia with an incidence of 26.9% with RTV. Elevated triglycerides and cholesterol occurred in 139.2% and 15% of patients respectively and were most commonly associated with RTV (58.2% and 28.4%). The overall incidence of lipodystrophy was 5.8%, being most commonly associated with IDV(10.3%). 19.8% of PI exposures were discontinued because of intolerance [ranging from 14% with SQV to 50.7% with RTV].
Conclusion: SQV$_{hgc}$ was the best tolerated possibly due to the poor bioavailability of this formulation. RTV, the most poorly tolerated of the PIs prescribed in our patient cohort, was associated with the highest incidence of ADRs and the highest discontinuation rate. Despite the fact that elevated triglycerides and cholesterol were most commonly associated with RTV, lipodystrophy occurred at the highest incidence in patients on IDV. This may possibly be explained by the high discontinuation rate in patients on RTV and the significantly shorter duration of exposure to RTV than IDV in this study (349 days and 462 days respectively).

Identifying the changing needs of an Irish HIV-infected cohort from 1995 to 1999*.

M Ryan, S Clarke, P Harrington, C Merry, M Barry, F Mulcahy.

STIs and the millennium: past, present and future. A joint meeting of the American Sexually Transmitted Diseases Association & Medical Society for the Study of Venereal Disease, Baltimore, Maryland. May 2000. Abstract 261.

St. James's Hosp., Dublin provides in-patient and out-patient care for the largest HIV-infected cohort in Ireland. 777 patients attended between 1/95 and 6/99. Demographic trends in new attendees were examined in order that the service could adapt to the changing needs of the cohort.
Method: A comprehensive database detailing patient demographics, antiretroviral history, disease indicators(viral RNA, CD4, AIDS defining illnesses) and hospital admissions has recently been constructed. Data was abstracted from patient charts, pharmacy records, and laboratory records. Results: Database analysis revealed the following demographic trends. There was an overall increase in the number of new attendees each year from 51 in 1995 to 84 in 1998 and a further substantial increase to 58 by 6/99. The proportion of new haemophiliac attendees increased from 2% in 1995 to 25% in 1996, falling to 11% and 2% in 1997 and 1998 and zero in 1999. The proportion of patients attending the service for the first time whose risk factor for acquisition was intravenous drug use (IDU) increased from 22% in 1995 to 50%in 1999*. The mean age of IDUs newly attending the service decreased from 31.6 years in 1995 to 26.1 years in 1999. The proportion of attendees who had acquired HIV heterosexually increased from 22% in 1995 to 26% in 1999* while the proportion of homosexuals fell from 51% to 24% over the same time period. Consequently whereas women represented 20.4% of new attendees in 1995, by 1999* the proportion of female new attendees had increased to 41.4%. The proportion of new attendees of Irish origin fell from 92% in 1995 to 78% in 1999* coincident with an increase in the proportion of new African attendees from zero % in 1995 to 12%in 1999*.
Discussion: Reasons for these changes in demographic characteristics of new attendees may include: a change in policy by the National Haemophilia Centre to refer haemophilacs to our clinic for HIV care; increased HIV testing of young IDUs by the Drug Treatment Service subsequent to centralisation of methadone maintenance in the latter half of 1998; Ireland's recently increasing refugee population, and adoption of a national ante-natal HIV screening program in 1998. This study illustrates changing demographic patterns amongst new attendees and facilitates adaptation of the healthcare and support services provided by our clinic to the changing needs of our patient cohort. In particular the needs of our increasing numbers of women, young IDUs and non-nationals for whom English is not a first language are being addressed.

1999*-data to 6/99 only.

The impact of triple antiretroviral therapy on treatment of MAC infection.

M Ryan, C Merry, M Barry, P Harrington, F Mulcahy.

Fifth Annual meeting of the British HIV Association, Cambridge. March 1999.

Triple antiretroviral therapy (TAT) replaced dual therapy as standard of care for the management of HIV infection due to an improved understanding of viral dynamics and the development of new classes of drugs(protease inhibitors, non-nucleoside reverse transcriptor inhibitors). A significant decrease in the rate of opportunistic infections (OIs) following widespread use of TAT has been reported. *Mycobacterium avium* complex (MAC) is a late stage indicator OI. Using drug expenditure reports for the HIV OPD pharmacy the change in epidemiology of MAC infection in our cohort in pre and post TAT eras (1995, 1998) was examined.

Results

	1995	**1998***
Drug Expenditure on MAC Tx.	39,652.41 EURO	25,366.81 EURO
No. of patients on Tx.	32	15
No. of new diagnosis	23	3
No. of patients deceased on Tx.	18(56%)	3(20%)

*projected from 11/98.

There is a statistically significant decrease in both the incidence of MAC and therefore in the annual expenditure on MAC treatment (Tx.). This is likely to reflect the effect of TAT in halting progression to advanced HIV disease. Patients who have already advanced to severe disease also benefit from the introduction of TAT as indicated by the reduced mortality in patients already on MAC Tx.

The impact of triple combination therapy on MAC infection.

M Ryan, C Merry, M Barry, P Harrington, F Mulcahy.

National Scientific Medical Meeting, Dublin. April 1999. Abstract 147.

Triple antiretroviral therapy (TAT) replaced dual therapy as standard of care for the management of HIV infection due to an improved understanding of viral dynamics and the development of new classes of drugs(protease inhibitors, non-nucleoside reverse transcriptor inhibitors). A significant decrease in the rate of opportunistic infections (OIs) following widespread use of TAT has been reported. *Mycobacterium avium* complex (MAC) is a late stage indicator OI. Using drug expenditure reports for the HIV OPD pharmacy the change in epidemiology of MAC infection in our cohort in pre and post TAT eras (1995, 1998) was examined.

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