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Title	Model of care for HIV infection in Ireland
Authors	Brennan, Aline
Publication date	2016
Original Citation	Brennan, A. 2016. Model of care for HIV infection in Ireland. PhD Thesis, University College Cork.
Type of publication	Doctoral thesis
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Coláiste na hOllscoile Corcaigh

MODEL OF CARE FOR HIV INFECTION IN IRELAND

A thesis submitted to the National University of Ireland, Cork for the degree of Doctor of Philosophy in the Department of Epidemiology & Public Health



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November 2016

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List of abbreviations

Abbreviation	Term
ADI	AIDS defining illness
AIDS	Acquired Immunodeficiency Syndrome
ARV	Anti-retroviral
CI	Confidence interval
COHP	Country of high prevalence
COI	Cost of illness (study)
CPI	Consumer price index
CUH	Cork University Hospital
CUMH	Cork University Maternity Hospital
DRG	Diagnosis related group
EMA	European Medicines Agency
GUM	Genitourinary medicine
(HA)ART	(Highly active) Anti-retroviral therapy
HIV	Human immunodeficiency virus
HPRA	Health Products Regulatory Authority
HPSC	Health Protection Surveillance Centre
HSE	Health Service Executive
HTA	Health technology assessment
ID	Infectious Disease(s)
IDU	Injecting drug user
MSM	Men who have sex with men
MMUH	Mater Misericordiae University Hospital
NIPO	National Information and Pricing Office
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
OLHSC	Our Lady's Hospital for Sick Children, Crumlin
PI	Protease inhibitor
PLHIV	People living with HIV
PPM	Per patient month
PPP	Purchasing power parity
SJH	St James's Hospital, Dublin
UCHG	University College Hospital, Galway
UHL	University Hospital, Limerick
WHO	World Health Organisation

Declaration

I declare that this thesis has not been submitted for another degree at this or at any other University. The work, upon which this thesis is based, was carried out in collaboration with a team of researchers and supervisors who are duly acknowledged in the text of the thesis. The Library may lend or copy this thesis upon request.

Signed_____ Date_____

Acknowledgements

I would like to sincerely thank my supervisory team, Prof Mary Horgan, Prof Colm Bergin and Prof John Browne for all your support and advice over the course of my PhD. I would also like to thank Dr Aisling O'Leary, who also provided invaluable supervisory support in the design and initial data collection phases of this research.

I would also like to thank the staff members of the HIV centres who participated in my research. In particular I would like to acknowledge all CUH staff members for their time and patience in answering my seemingly unending list of questions, especially Dr Arthur Jackson, Dr Gabriella Rizzo, Liz Murphy, Jacinta Joyce, Fiona Ahern, Marih O'Leary and Andrew Murphy. Thanks also to Tina who not also endured my questions but also shared her office with me for weeks on end while I collected data. Thanks also to all the administrative staff of UCC, CUH and the SPHeRE programme who provided me with assistance at various times: Rachel Hyland, Melissa Walsh, Vicky Murphy, Tara O'Connell, Dervla Hogan, Margaret O'Flaherty, Michelle Syron, Elaine Healy and Carlos Bruen to mention but a few.

I would also like to thank everyone in the Department of Epidemiology and Public Health, particularly Aoife and Peter for the company on the train up and down to Dublin that first year, and my cubicle/office mates over the years; Martin, Margaret, Fiona, Sarah-Jo and Christina, as well as to the other students in my HRB cohort for all those coffee breaks and lunches that kept me relatively sane.

Finally I would like to thank my family: my parents and siblings for their never ending support and encouragement, particularly my father for all the proof reading; my daughters, Alice and Rebecca for inspiring me; and of course, my husband Denis, without whose support I would never have started, let alone finished a PhD.

Thesis abstract

Background

Highly active anti-retroviral therapy (HAART) has completely transformed the clinical course of HIV. HIV is now considered a chronic disease, with patients living for decades on treatment. It is anticipated that health services will be placed under increasing pressure as the prevalence and age profile of the HIV population increases. A deeper understanding of the specific factors driving the use and cost of HIV care in Ireland is needed to allow quantification of future resource needs as well as the identification of potentially cost-effective service delivery modifications. This thesis investigates the current use and direct cost of hospital care by HIV patients, and explores some of the patients and clinic level factors influencing the cost of HIV care in Ireland.

Methods

The total number of patients in care annually as well as the changing age profile of patients over time was estimated using routine data on the number of notified cases and general mortality in combination with published estimates of HIV related deaths. Current resource use and costs of care in 2012 were estimated from two studies carried out in the HIV centre located in Cork University Hospital. The first study estimated the total cost of outpatient HIV care using micro-costing, including data on HAART use and cost. The second study used data extracted from the finance department of Cork University Hospital to identify and describe the pattern of use and non-drug cost of all hospital services (including inpatient episodes, non-ID outpatient appointments and emergency department attendances) by HIV patients in 2012. A national estimate of the cost of ambulatory HIV care in 2012 was then generated adjusting the estimated unit costs of outpatient visits, for variation in service delivery across the six centres providing adult HIV care in Ireland in 2012 and using national anti-retroviral sales data.

Results

The number of HIV patients accessing HIV care was estimated to be 3,820 in 2012, with 18% of patients aged ≥50 years. Assuming the rate of new diagnosis remains stable we estimated that the number of patients in care will have increased by 40% to 4,607 by 2020 and that the proportion of patients aged ≥50 years will have increased to 30%.

HAART is the overwhelming driver of the cost of outpatient HIV care. Treatment costs accounted for 90% of the total cost of outpatient HIV care estimated in the micro-costing study. Patient factors associated with increased total outpatient HIV

costs on multivariate analysis were younger age (< 50 years), female gender and being on HAART but not suppressed. When categories of costs were examined separately older patients were found to have both significantly lower HAART costs as well as HIV outpatient visit costs while female patients only had significantly higher HAART costs. On analysis of non-drug hospital costs (i.e. including inpatient admissions, non-ID outpatient appointments and emergency department attendances) low CD4 count and treatment status were significant, but no demographic factors were identified. A small number of patients (2%) with very low CD4 counts incurred a disproportionate amount of inpatient (61%) and total hospital non drug costs (31%).

Extrapolating from the micro-costing estimates and taking into account variation in service delivery across centres, we estimate that the annual non-drug cost of providing ambulatory HIV care in Ireland in 2012 was €1,127 per patient or €4.31 million, and that including HAART, the cost to the health service provider in 2012 was approximately €50 million.

Discussion

The age profile of HIV patients in care is increasing in Ireland at a similar rate as in other developing countries. However, in contrast to what has previously reported in the literature, older patients in our study did not appear to incur increased total costs compared to their younger counterparts. The main reason for this was that the older patients were on less expensive treatment regimens, and HAART cost is the main driver of total cost of outpatient HIV care. Exactly why this was is unclear, but regimen choice is influenced by many health-system (e.g. drugs available, clinician preference etc) as well as patient factors (treatment history, resistance, patient preference etc). There was also no difference identified in the non-drug cost of care for older patients. This may have been due to the patients themselves being possibly younger and/or healthier than in other published studies, but may also be due to a lack of co-ordinated routine screening for age-related comorbidities in HIV patients in Ireland, as well as the cost estimates being based on data collected in a single centre which did not include costs incurred in other hospital, community and primary care settings. As the increasing age and total number of patient increases demands on HIV services it is imperative that measures to improve service efficiency are evaluated in terms of both clinical outcomes and costs. Interventions such as increased screening to reduce the number of patients diagnosed with advanced disease and increased use of generics have the potential to generate cost-savings, however a nationally co-ordinated approach is needed to drive such changes while ensuring the current standard of care is maintained.

1 Introduction & Background

1.1 Introduction

This thesis is comprised of a number of papers presenting research on the patterns, determinants and cost of hospital resource use by HIV patients in Ireland (Figure 1-1).

Firstly a background chapter provides a brief description of the epidemiology, care and treatment of HIV, both in Ireland and internationally. This is followed in the second chapter by modelled estimates of the total number and age breakdown of HIV patients in care in Ireland. The results of a systematic review of the literature to identify the determinants of utilisation of outpatient HIV services are presented in Chapter 3. Chapter 4 reports the results of a micro-costing study carried out in the Infectious Diseases outpatient clinic of CUH, while the patterns of utilisation of all hospital services by HIV patients attending Cork University Hospital (CUH) in 2012. are presented in Chapter 5. In Chapter 6 the variation in clinical practice between HIV centres is described and national estimates of the cost of HIV care to the Health Service Executive are estimated, taking into account this variation. In the final chapter there is an overall discussion of the main findings including the strengths and weaknesses of this thesis. The policy implications of this research are also discussed, and possible areas of future research are identified.

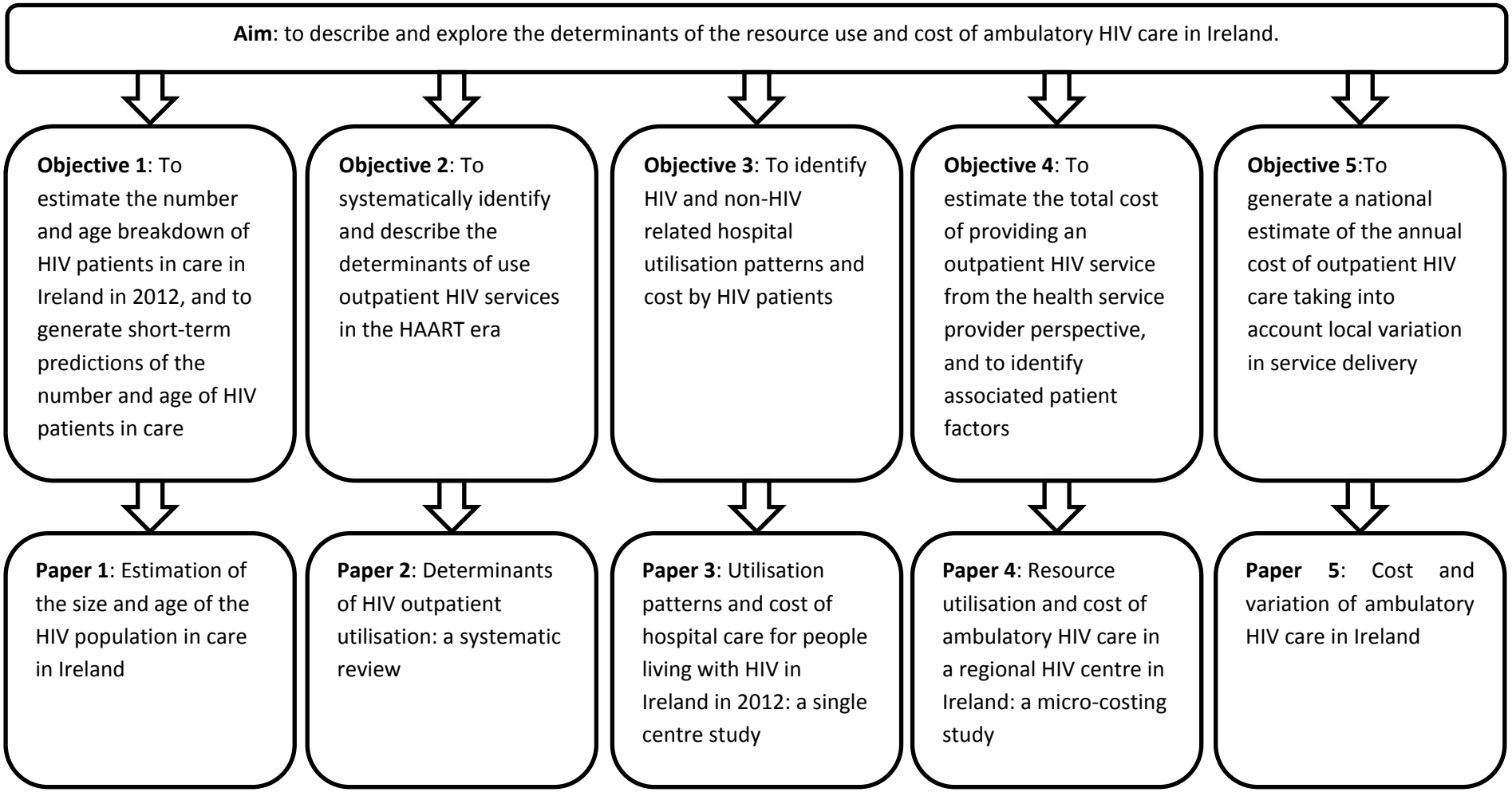


Figure 1-1. Thesis outline schematic

1.2 Background

The first cases of what was to become known as Acquired Immunodeficiency Syndrome (AIDS) were reported in the United States in 1981 [1]. Since then, the World Health Organisation (WHO) estimates that almost 78 million people have been infected with the Human Immunodeficiency Virus (HIV) which causes AIDS and about 39 million people have died as a result of HIV/AIDS [2].

1.2.1 Natural history

The clinical course of untreated HIV infection varies considerably. On initial infection 40%-90% of patients display symptoms of an acute illness, called acute retroviral syndrome or primary HIV infection [3]. However, the clinical symptoms during this phase are usually non-specific and a relatively small proportion of HIV infections are diagnosed at this stage, even in those known to be at high risk of infection [4]. This is followed by a long period of asymptomatic infection during which the number of CD4 T-lymphocytes in the blood (CD4 count) declines gradually by about 50-100 cells/µl per year (Figure 1-2). In the absence of treatment the median time from infection to developing AIDS is around 10-11 years, although the rate of progression varies considerably [5]. Once the CD4 count drops below 200 cells/µl or an AIDS-defining illness (ADI) has been diagnosed the patient is considered to have AIDS [6]. The median survival time of untreated AIDS is 12-20 months [7]. In the absence of treatment viral load (number of copies of viral RNA per ml plasma) strongly predicts the rate of CD4 decrease and progression to AIDS and death [8].

Effective treatment (highly active anti-retroviral therapy or HAART), which supresses viral replication, has been available since 1996. HAART has dramatically improved the prognosis for people infected with HIV and if treatment is started early enough patients now have a near normal life-expectancy [9]. Despite this, HAART is not curative and treatment is lifelong. Patients on treatment require close monitoring due to the possibility of adverse events such as toxicity and/or development of resistance.

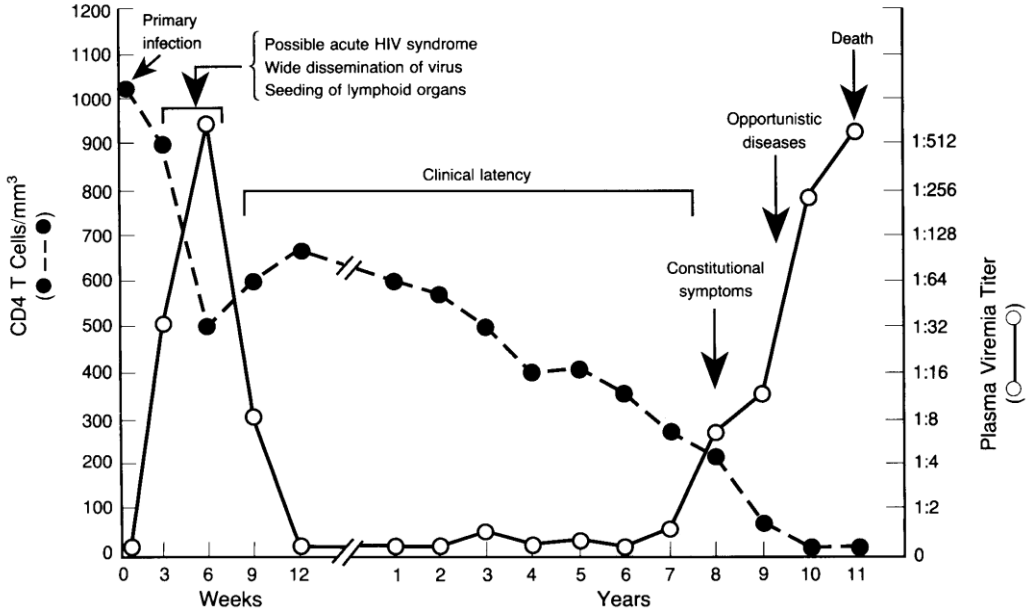


Figure 1-2. Typical course of untreated HIV infection (reproduced with permission from [10], copyright Massachusetts Medical Society)

1.2.2 Global epidemiology

The first cases of AIDS were reported in men who have sex with men (MSM) in the United States in 1981 [1]. It rapidly became apparent that this new disease was already widespread both within the US and throughout the world [11-16]. Within two years the causative agent, later named HIV, had been identified [17,18], and by 1985 a diagnostic test for HIV antibodies was commercially available [19].

Although first described in the US [1], it has since been established that the virus originated from cross-species transmission(s) of simian-immunodeficiency virus(es) from non-human primates to humans in central Africa as early as the 1920s [20,21]. Around 1960 the growth rate of new infections seems to have increased substantially and cases started spreading more widely throughout the rest of the world [21,22]. Since then sub-Saharan Africa has continued to suffer disproportionally from HIV (Figure 1-3).

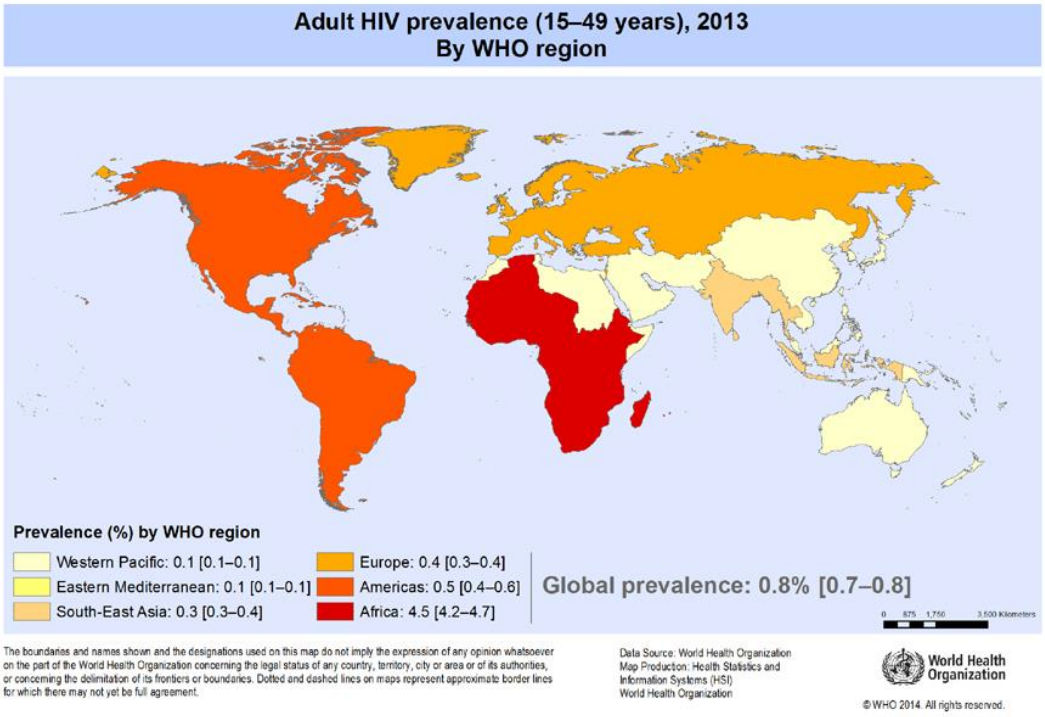


Figure 1-3. Global prevalence of HIV infection[2]

In recent years, as a result of global prevention and treatment efforts, the incidence of new cases of HIV and AIDS-related deaths worldwide have started to decrease. However the prevalence of HIV continues to increase as a result of the decline in mortality (Figure 1-4), with an estimated 35 million people living with HIV in 2012 [23]. The age profile of the epidemic is also changing as people are living longer

with HIV infection. The proportion of people living with HIV who are over 50 years of age is increasing across all regions of the world, but most dramatically in developed countries, where it is estimated that one third of adults living with HIV in 2012 were aged 50 years or older [24,25].

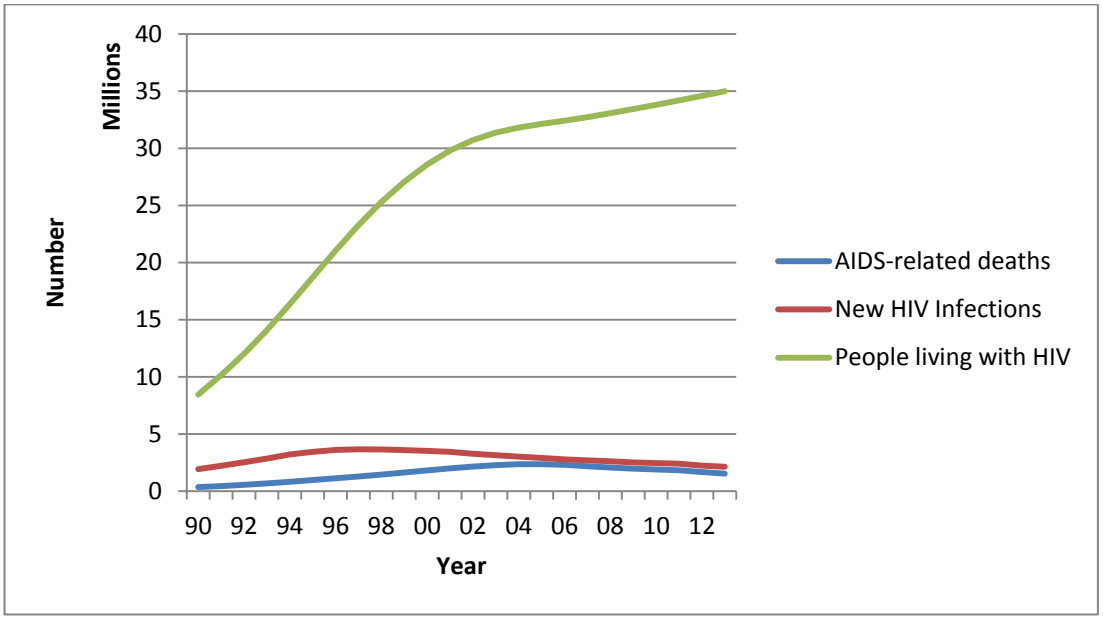


Figure 1-4. Number of new HIV infections, AIDS related deaths and people living with HIV globally [26]

1.2.3 HIV treatment and care

1.2.3.1 Treatment

Initially the only treatments available for patients with HIV/AIDS were prophylactic treatments to prevent opportunistic infections (OIs). A number of nucleoside reverse transcriptase inhibitors (NRTIs) were trialled, alone and in combination in the late 1980s and early 1990s, however their effectiveness was found to be limited [27-32]. It was not until drugs from two new classes, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) became available in the mid-1990s that a real breakthrough was made in HIV treatment. Trials of triple

therapy (HAART) consisting of either a PI or an NNRTI combined with two NRTIs were found to give substantially better results than previously available therapies [33-35]. Subsequent observational studies showed a sharp decline (60%-80%), in AIDS, hospitalisations and deaths following the introduction of HAART into clinical practice [36,37]. Since then additional classes of drugs have been developed which target other stages of the HIV virus lifecycle: fusion inhibitors, entry inhibitors and integrase inhibitors (Figure 1-5). Although effective, the early HAART regimens were arduous for patients, with multiple tablets with varying requirements and significant side-effects. Since then more tolerable formulations and simplified regimens have been developed and have resulted in improved adherence [38], for instance several single-tablet regimens, which combine 3 or 4 drugs into a single daily tablet, are now available [39].

Eligibility criteria for treatment have traditionally been based on a patient's CD4 count as well as other factors including readiness for treatment and the likelihood of onward transmission of infection. However, due to evidence regarding the clinical benefits of early HAART treatment and the reduction in transmission of HIV in patients on treatment, international guidelines have moved towards recommending treatment of all patients regardless of CD4 count [3,40-42].

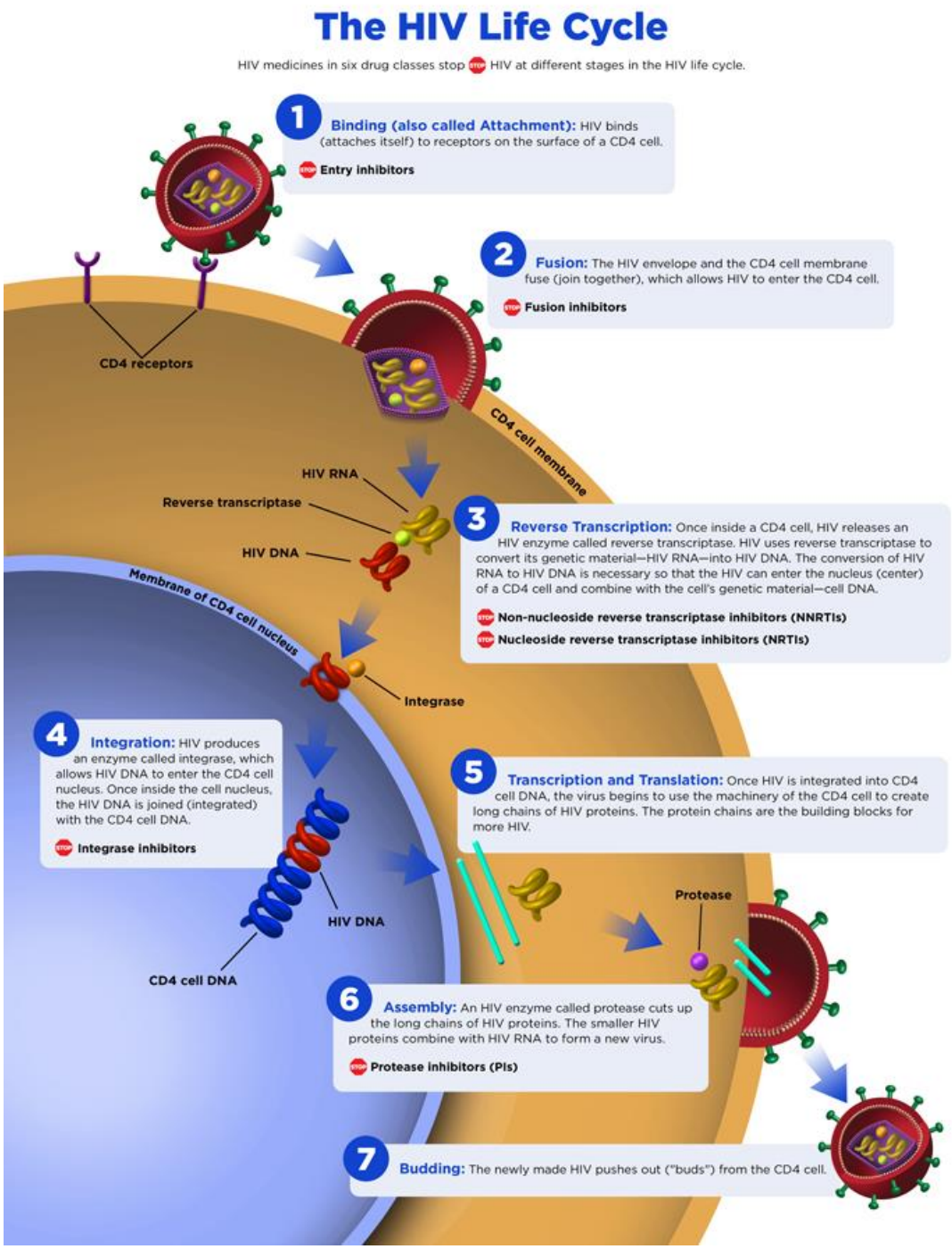


Figure 1-5. Life cycle of HIV virus and anti-retroviral treatment targets [43]

The success of treatment with HAART is measured in terms of the reduction of viral load [44,45], preferably to undetectable levels (or <50 copies/ml) within six months of initiating treatment [3,40-42]. Virological failure is considered to occur if viral suppression is not achieved within 6 months of starting therapy in persons that remain on treatment, or if the viral load of a patient on HAART that was previously suppressed increases beyond a defined level (the precise definition of which varies by guideline) [3,40-42]. Virological failure may occur for a variety of reasons including suboptimal adherence, medication intolerance, pharmacokinetic issues and resistance [3].

1.2.3.2 Setting and organisation of care

In the HAART era, routine HIV care has tended to be provided by HIV specialist services, due to the complex nature of the treatment (e.g. possibility of resistance, toxicity and drug-interactions). However the setting and organisation of care can vary depending on the local health care system and HIV epidemiology.

There is clear evidence that the best patient outcomes are achieved when care is provided by experienced and expert providers [46]. In developed countries the primary care provider tends to be a specialist doctor, however in some countries care is shared (in varying degrees) between specialists and primary care [47-51]. Research has also shown that with appropriate support the cadre of staff providing HIV care may be less important than their level of experience [52].

While HIV clinics are often located in hospital settings, there is no evidence that clinics need to be located in a hospital setting to provide high quality care. Studies looking at patient outcomes in hospital and non-hospital based clinics have found

no difference in patient outcomes [53,54] and decentralisation of HIV care from hospitals to more peripheral health facilities (often implemented in conjunction with task-shifting) has shown no evidence of poorer patient outcomes in the developing world [55]. It is important however, that HIV care providers have sufficient volumes of patients to maintain the expertise of staff as smaller centres have been found to have poorer patient outcomes, although the threshold is not entirely clear [56,57].

Integration of HIV services into antenatal/maternal/child health settings, TB services and opioid substitution-centres, has also been associated with improved HAART uptake and retention in care [40], although the evidence regarding the economic benefits of integrating HIV care and treatment into general health services and services for vulnerable populations (sex workers, mental health and or substance abuse service users) is weak and the benefits unclear [58].

1.2.3.3 Care cascade

As the availability of effective treatments has transformed the outcome of HIV infection, attention has turned towards the challenge of maximising the proportion of patients being successfully treated. There are multiple hurdles along the path to successful treatment. Due to the number of steps at which patients can drop out of this process HIV care has been likened to a “leaky pipe” [59]. The end result is that a surprisingly small proportion of people living with HIV are virally suppressed, with figures from the United States and Australia as low as 20%-35% [60-62], although rates in Northern European countries appear to be higher at around 50%-60% [62].

The first point in the cascade of care is diagnosis. Late diagnosis (defined as a CD4 count < 350 µl/ml or an ADI at diagnosis [63]) is associated with poorer outcomes [64,65]. Timely diagnosis is not only beneficial for the individual, but also has an important role in the reduction of onward HIV transmission [66,67] as knowledge of a HIV positive status is associated with a reduction in high-risk sexual behaviour [68]. However, timely diagnosis continues to be a challenge worldwide [69-71] and it is estimated that as many as 35% of people with HIV in Western Europe are not aware of their infection [72]. Some of the reported reasons why diagnosis can be delayed include the asymptomatic nature of HIV infection, the perception (of individuals and/or clinicians) that the person is not at risk of HIV, fear of diagnosis and the associated stigma, and lack of knowledge of healthcare rights and/or language difficulties especially in the case of migrants [69].

Once diagnosed, patients' engagement in care can vary along a continuum (Figure 1-6). Patients need to be linked into care promptly following their initial diagnosis. In the US approximately 75% of patients are linked into care within 6-12 months of diagnosis [73], while in Europe a smaller proportion of patients, around 8%, appear to have delayed entry to care (> 3 months after diagnosis) [65]. Once in care, patients require regular monitoring, regardless of whether or not they are on treatment [40,74,75]. Monitoring of patients' general health, immune status, and viral load (if on HAART) ensures that treatment can be started promptly and that any health problems are identified at an early stage. Early linkage and adherence to HIV care are associated with improved outcomes [76], however there is still some debate on the optimal frequency of monitoring needed [77,78]. Data from the UK

have shown that around 5% of patients drop out of care each year, and a further 4.2% attended intermittently (i.e. not every year) [79].

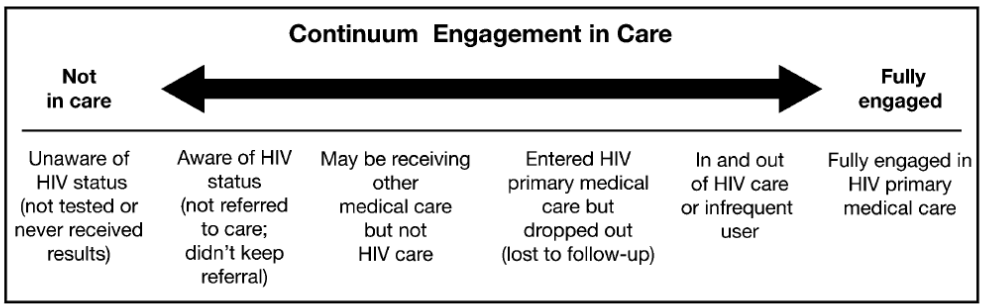


Figure 1-6. HIV continuum of care (reprinted from [80] with permission)

1.2.4 HIV in Ireland

1.2.4.1 Epidemiology

Incidence

The first cases of AIDS were reported in Ireland in 1982 [81]. Since HIV testing became available (in 1985) 6,629 people have been diagnosed with HIV in Ireland [82].

In the early years of the epidemic, HIV infections were concentrated in the injecting drug user population (IDUs). However, over time the risk profile of newly diagnosed cases has changed (Figure 1-7), and in recent years there has been a steady increase in the numbers of new diagnoses who are men who have sex with men (MSM).

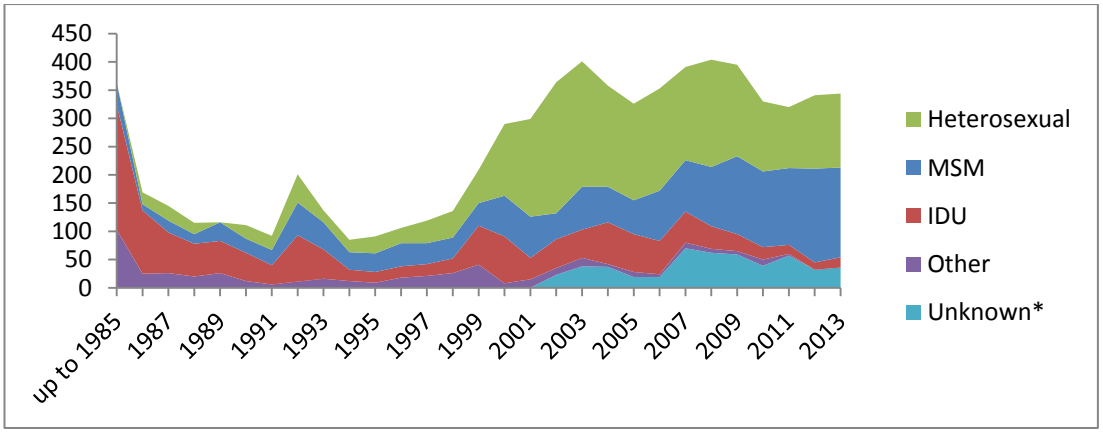


Figure 1-7. Number of reported cases of newly diagnosed HIV in Ireland by risk group

Sources: pre 2000 data [83], from 2000 onwards, HPSC annual reports. *until 2000 "unknown" were included with "heterosexual", in 2012 and 2013 "other" were included with "unknown".

Prevalence

While quite detailed information is available on new diagnoses of HIV particularly since 2003 (when a voluntary national HIV surveillance system was introduced), less information is available on the prevalence of HIV in the general population in Ireland. UNAIDS estimates the figure at between 6,300-10,000 people living with HIV in 2012 (0.1%-0.2% of the population) [23]. The UNAIDS estimates for countries with concentrated epidemics rely on accurate information on the size of high risk groups and the prevalence of HIV within those groups, if these data are lacking the estimates may not be accurate [84]. A prevalence study of people in care in Ireland found 3,254 were attending for HIV care in 2009/2010 [85]. The discrepancy between these figures may be explained by possible inaccuracy of the estimates, as well as the proportion of people who are undiagnosed or who are not accessing care.

Information on the prevalence of HIV in the general population is available from the routine screening of two groups: antenatal women and blood donors. The

proportion of antenatal women who are HIV positive has been decreasing steadily since surveillance started from 0.32% in 2002 to 0.14% in 2013 [86]. The reported prevalence in blood donors is lower, at 0.005% [87]. HIV prevalence in antenatal populations is generally higher than the general population (as they have, by definition, had unprotected sex) while the eligibility criteria for blood donation means that the proportion of new blood donors testing positive is generally lower than that of the general population.

Various surveys describing the HIV prevalence in different high risk groups have also been carried out in Ireland (Table 1-1).

Table 1-1. Estimates of HIV prevalence in high-risk populations in Ireland

Population	Subgroup	Prevalence rate	Year	Reference
A&E attenders		0.29%	2013	[88]
Prisoners	All IDU Non-IDU	2.0% (1.3%-3.0%) 3.5% (2.1%-5.5%) 0.9% (0.3%-1.9%)	1998	[89]
IDUs	Needle-exchange clients	14.8%	1991	[90]
	Addiction treatment centre attendees	16.7%	1997	[91]
	Dublin (in treatment and not in treatment)	8.4%	1997 (year of publication)	[92]
	Self-reported	24.8%	2000	[93]
	Addiction treatment centre attendees	11%	2001	[94]
	A&E attendees	13.8%	2010	[95]
Asylum seekers		2.2%	2000-2003	[87]
		1.7%	2004-2012	[96]
MSM (self-reported)	Ever tested for HIV All surveyed	4.8% 2.5%	2005-2006	[97]
	Ever tested for HIV All surveyed	9.5% 6.0%	2010	[98]
Homeless		6%	2005	[99]
Prostitutes	Dublin – attending a drop-in clinic	2.5%	1991-1997	[100]

Routine morbidity and mortality data

Between 2005 and 2012 there have been on average 824 (range 664-1,131) admissions per year containing a diagnosis of HIV, in 23% of these HIV has been the primary diagnosis (average 186 admissions per year, range 139-287) [101].

HIV/AIDS has only been recorded as a specific cause of death in routine mortality statistics since 2007, since then (up to 2014) 96 deaths have been attributed to HIV/AIDS [102-109]. Deaths in people with HIV infection were also reported to the Department of Health/HPSC through the voluntary HIV surveillance system. By 2011 approximately 505 deaths in people with HIV had been reported from the start of the epidemic under this system, however not all these deaths were necessarily HIV-related (personal communication Dr Kate O'Donnell 22/04/2015). Since 2012 surveillance data is only collected on deaths which occur at the time of HIV diagnosis.

1.2.4.2 Development and organisation of HIV care in Ireland

In the early 1990s two reports were published which influenced how HIV services developed in Ireland, one by Comhairle na n-Ospidéal [110] and the other by the National AIDS Strategy Committee (NASC) [81].

Comhairle na n-Ospidéal

Comhairle na n-Ospidéal was a statutory body set up under the Health Act 1970 to regulate the appointment of consultant medical staff and to specify the qualifications for such appointments. It also advised the Minister for health on

matters relating to the organisation and operation of hospital services (it was dissolved by the Health Act 2004 and its functions were transferred to the HSE) [111]. In March 1992 Comhairle na n-Ospidéal published its report "AIDS at consultant level" [110]. Its terms of reference included making recommendations "…on mechanisms to improve the management of AIDS patients at consultant level and to clarify the role of the different specialities in the services for persons who are HIV positive and/or who have AIDS" [110]. At this time it was government policy that persons with HIV/AIDS should receive care appropriate to their needs in both community and institutional settings and that each acute hospital was responsible for HIV/AIDS cases requiring hospital care in their catchment area [110]. In practice St James's hospital (SJH) was seeing the vast majority of AIDS cases at the time of this report although a small number of cases had been seen in Cork Regional Hospital (now CUH), the Mater Misericordiae Hospital, Beaumont Hospital, Our Lady's Hospital for Sick Children Crumlin (OLHSC), and the Coombe and Rotunda maternity hospitals. Respite care for AIDS patients was provided in Cherry Orchard Hospital. SJH became the de facto HIV centre in Ireland as the only consultant in genitourinary medicine (GUM) in Ireland at that time was based there. In addition the national haemophilia centre was located in SJH and the hospital's catchment area had a high prevalence of injecting drug users [110]. HIV/AIDS patients in other hospitals were seen by a mixture of physicians, mainly general physicians, respiratory physicians and gastroenterologists [110].

This report concluded that inpatient care for HIV/AIDS patients should be concentrated at a small number of large multi-disciplinary general hospitals and

recommended the appointment of four additional Infectious Disease (ID) consultants in the Dublin area (to be shared between SJH, St Vincent's Hospital, the Mater Misericordiae Hospital and Beaumont Hospital with sessional commitments to the public maternity hospitals and Cherry Orchard), as well as ID consultant posts in both Cork and Galway with consideration for another ID consultant post in Limerick in the future. The report also recommended the appointment of a GUM consultant to be based in the Mater Misericordiae Hospital and identified that a second GUM consultant may be needed in SJH in the near future.

National AIDS strategy Committee

A National AIDS Strategy Committee (NASC) was established in 1991 with a remit covering care and management (including primary care), surveillance, education and prevention, and discrimination. Four sub-committees were established to look at each of these areas, and their first report was published in 1992 [81].

The terms of reference of the Care and Management Sub-committee were "To consider the development of appropriate arrangements for the care and management of persons with HIV/AIDS at primary care and hospital levels including the development of liaison arrangements between the prison, health and welfare systems. The development of policy recommendations should be carried out in co-ordination with the Committee on Infectious Diseases in Prisons established by the Minister for Justice" [81].

The main care-related recommendations of this report were that care for patients with less advanced disease should be provided in the community, by general

practitioners with appropriate supports and/or in satellite clinics to be established outside the hospital setting to provide primary and preventive care for HIV patients and drug users. Strengthening of community services and additional resourcing of voluntary agencies was also recommended.

Within a few years of the publication of this report however the landscape of care required by HIV patients had completely changed, thanks to the development of HAART, and it was no longer considered feasible for HIV patients to be cared for in primary care. Routine HIV care needed to be provided in specialist facilities on an outpatient basis due to the complex drug-treatments and monitoring required [83]. A second NASC report, published in 2000, reviewed the progress on the previous reports recommendations and reported that four ID consultants had been appointed since the previous report, one each in SJH, OLHSC and CUH and one shared between the Mater Misericordiae University Hospital (MMUH) and Beaumont Hospital [83]. By 2005 there were nine ID/GUM consultants in Ireland, including one in University College Hospital Galway (UCHG) [112], and an infectious diseases consultant was appointed in University Hospital Limerick (UHL) in 2008.

In 2012 in Ireland adult HIV-care was provided by six specialist centres, three in Dublin (SJH, MMUH and Beaumont Hospital) and three located around the rest of the country (CUH, UCHG and UHL). In 2015 a HIV service was also established in St Vincent's hospital. Paediatric HIV care is provided in Our Lady's Hospital for Sick Children, Crumlin (OLHSC). Routine care is provided on an outpatient basis by multidisciplinary teams including at a minimum a consultant in infectious disease/genitourinary medicine, non-consultant hospital doctors, nursing staff, and

clerical staff. Some of the centres are also supported by HIV pharmacists and other allied health professionals (social workers, dieticians etc) [112]. Care is based on international best-practice guidelines, which are regularly updated in response to emerging evidence on more efficacious treatments, timing of treatment initiation, care delivery pathways and cost-effectiveness evaluations.

1.2.4.3 Treatment

The European Medicines Agency (EMA), grants marketing approval for all new HIV/AIDS treatments through a compulsory centralised procedure which covers all EU member states [113]. In addition, the Irish Health Products Regulatory Authority (HPRA) can grant national approval for products that are exempt from the centralised procedure. The list of drugs currently approved by the EMA and/or the HPRA for treatment of HIV infection are shown in Table 1-2.

There are currently four generic anti-retrovirals (ARVs) approved for use in Ireland although only one, nevirapine, appears to be available for sale currently (personal communication, CUH HIV pharmacist 15/05/2014). The fixed dose combination of Emtricitabine / tenofovir disoproxil fumarate (Truvada®) is also due to come off patent in 2017.

Table 1-2. List of medications for treatment of HIV infection approved for use in Ireland [114,115]

Active Substance	Authorisation date		Notes
	First	Generic	
Multi-class combinations			
Abacavir sulfate / dolutegravir sodium / lamivudine	01/09/2014		
Efavirenz / emtricitabine / tenofovir disoproxil fumarate	13/12/2007		
Elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate	24/05/2013		
Emtricitabine / rilpivirine hydrochloride /tenofovir disoproxil fumarate	28/11/2011		
NRTIs			
Abacavir	08/07/1999		
Abacavir / lamivudine	17/12/2004		
Abacavir (as sulfate) / lamivudine / zidovudine	28/12/2000		
Emtricitabine	24/10/2003		
Emtricitabine / tenofovir disoproxil fumarate	21/02/2005		
Lamivudine	08/08/1996	10/12/2009	
Lamivudine / zidovudine	18/03/1998	28/02/2011	
Stavudine	08/05/1996		
Tenofovir disoproxil fumarate	05/02/2002		
Zalcitabine	14/04/1994		Withdrawn 30/11/2005
Zidovudine	08/06/1987		
NNRTIs			
Didanosine	15/09/2000		
Efavirenz	28/05/1999	09/01/2012	
Etravirine	28/08/2008		
Nevirapine	05/02/1998	30/11/2009	
Rilpivirine hydrochloride	28/11/2011		
Protease Inhibitors			
Amprenavir	20/10/2000		Withdrawn 29/04/2010
Atazanavir sulphate	02/03/2004		
Darunavir	12/02/2007		
Darunavir / cobicistat	19/11/2014		
Fosamprenavir calcium	12/07/2004		
Indinavir sulphate	04/10/1996		
Lopinavir / ritonavir	20/03/2001		
Nelfinavir	22/01/1998		Withdrawn 23/01/2013
Ritonavir	26/08/1996		
Saquinavir	04/10/1996		
Tipranavir	25/10/2005		
Integrase inhibitors			
Dolutegravir	16/01/2014		
Elvitegravir	13/11/2013		
Raltegravir	20/12/2007		
Fusion/Entry Inhibitors			
Enfuvirtide	27/05/2003		
Maraviroc	18/09/2007		
Booster			
Cobicistat on silicon dioxide	19/09/2013		

1.3 Cost of providing HIV care

The distribution of healthcare costs has changed as patient outcomes have improved. The proportion of costs due to in-patient HIV-related care has decreased, while outpatient (and non-HIV inpatient) costs have changed little and drugs costs have increased [116].

1.3.1.1 Drug costs

HAART is the single biggest driver of cost. Although the generic manufacture of some ARVs as well international pressure on drug companies has resulted in a reduction in the cost of treatment from around US$10,000-15,000 per patient year in the early HAART era [117] to US$115 per patient year in 2013 in low and middle-income countries [118]. However, in high-income countries HAART still costs around €10,000-€15,000 per year per patient for first-line regimens [3,119] and accounts for between 50%-90% of the total direct healthcare cost of HIV [120-125]. The proportion of total costs due to HAART has also tended to increase over time, as the proportion of patients on treatment increases and newer (more expensive) drugs become available [119,124]. As more ARVs are due to come off patent in the coming years [126] the possible reduction in drug costs by replacing branded drugs with generic versions appears very appealing [119,127], although concerns exist about the possible detrimental effect on treatment adherence if branded single tablet regimens are replaced by generic multi-tablet equivalents.

1.3.1.2 Outpatient costs

Although the unit costs of an individual outpatient visits are low, because the bulk of HIV care is now provided on an ambulatory basis, the total cost of providing

ambulatory care often exceeds the cost of in-patient care [123,128]. An effective and efficient outpatient service is crucial in providing high quality care for chronic diseases such as HIV, in theory enabling the early identification and treatment of problems and thereby reducing hospitalisation rates.

Several extensive literature reviews of the costs of HIV in the HAART era have been carried out [122,125,129-131]. The conclusions from these reviews have been limited by the difficulties in comparing costs across studies due to differences in methodology (e.g. types of care and cost components included) and healthcare systems. These reviews have generally called for better reporting of cost data and the use of standardised methods [122,125,129,130].

The healthcare costs of HIV increase with more advanced disease [122,129], and late diagnosis [132,133], age [134] and co-morbidities [135,136] have also been associated with increased costs. Evidence regarding the role of other factors (gender, risk group, immigrant status) is less clear [121,137-139]. Although healthcare factors are also important determinants of health costs, less data are available on their impact on the cost of HIV care [140].

Modelling studies have projected substantial increases in the cost of providing treatment and care for HIV patients in the coming years [141,142] due to the increasing number of people living with HIV as well as expected increases in the use of second-line and salvage regimens as the patient population becomes more treatment experienced.

1.3.1.3 Cost of HIV care in Ireland

One previous study has been carried out reporting the cost of HIV care in Ireland. This study looked at HIV healthcare utilisation and cost in the early HAART era (1995-1999) in a single centre in Dublin [143] and documented the changes in healthcare utilisation patterns associated with the introduction of HAART. They estimated the total cost of HIV care to be IR£8,204 per patient year in 1999 (equivalent to approximately €20,000 in 2012), with approximately 50% of all costs in 1999 due to HAART, 30% due to inpatient care, and 20% to outpatient care [143].

1.3.2 Challenges for the future

HIV services are coming under increasing pressure, due to the sheer volume of providing routine HIV care combined with the increasing prevalence of age-associated chronic diseases [144]. HIV services will need to become more efficient in order to cope with the anticipated increases in demand without compromising patient care. It is currently unclear how this can best be achieved.

Evidence from resource-limited settings has suggested that HIV treatment can be successfully, and potentially cost-effectively, delivered in a variety of settings and/or by differing cadres of health care workers [55,145-147]. While in developed countries, there have been calls for increased involvement of primary care in the routine care of HIV patients [148,149] in line with models of care for non-communicable chronic diseases [150]. However, a recent review found very limited data supporting the clinical effectiveness or acceptability of HIV shared care in developed countries and none of the included studies reported comprehensive cost implications [50]. Reviews of other HIV health service interventions have reported

evidence supporting the effectiveness of some types of interventions aimed at medication adherence [151,152], linkage and/or retention in care [153,154] and decision support/clinical information systems [155]. Again however data on the cost implications of these interventions is very limited [58,146,151,156,157].

Other approaches for reducing costs while maintaining existing service configurations, have been suggested in terms of both reducing the cost of treatment [119,127,158-162] and reducing the cost of laboratory and/or clinical monitoring [77,119,146,157]. The underlying assumption of these approaches is that patient outcomes would not be affected by changes in regimens prescribed and/or reductions in monitoring. In reality full economic evaluations including both clinical and cost data need to be performed for the cost-effectiveness of these interventions to be established. As data on clinical effectiveness and costs may not be generalizable from one setting to another [163] it is important that local data on unit costs and current resource use be available in order to accurately assess the impact of such changes.

1.4 Overview of the thesis

Healthcare providers are now looking for innovative ways of improving the efficiency of their HIV services, in order to continue providing high quality care in the context of increasing demands but finite resources. In particular interest is growing in finding more efficient ways of delivering routine care to the large proportion of stable, virally suppressed patients.

While clinical need is a major determinant of the resources used by an individual patient, factors at all levels, patient, hospital and health system, can influence the cost of providing that healthcare.

High quality information on current service delivery models, resource utilisation patterns and cost of providing outpatient HIV care is vital in order to evaluate the financial impact of changes in the disease epidemiology and/or organisation of or services. Extrapolation from published international costing and burden of illness studies to the Irish setting introduces uncertainty into the outcomes, and may diminish the validity and rigour of future cost-effectiveness analyses that should rely on robust costing inputs specific to this setting. This may have a material impact on decision-making. The current, overall cost to the state of HIV disease in Ireland is unknown, although reliable individual constituents such as drug costs are available. While care in Ireland is based on international best-practice, anecdotal information suggests that there are subtle variations in management between centres. In light of the changing epidemiology of HIV, and the possibility of changing clinical management, it is vital that accurate cost data are available to enable appropriate planning of HIV services in Ireland for the future.

This thesis describes current use and cost of hospital care by HIV patients in Ireland, and explores some of the patient and clinic level factors influencing the current cost of HIV care.

1.4.1 Aim and objectives

The aim of this study is to describe and explore the determinants of the resource use and cost of ambulatory HIV care in Ireland.

This thesis has five primary objectives.

Primary objectives:

1. To estimate the number and age breakdown of HIV patients in care in Ireland in 2012, and to generate short-term predictions of the number and age breakdown of HIV patients in care up to the year 2020.
2. To systematically identify and describe the determinants of the use of outpatient HIV services in the HAART era.
3. To identify HIV and non-HIV related hospital utilisation patterns and cost by HIV patients
4. To estimate the total cost of providing an outpatient HIV service from the health service provider perspective, and to identify associated patient factors.
5. To generate a national estimate of the annual cost of outpatient HIV care taking into account local variation in service delivery.

1.4.2 Clarification of researcher's role

This is an original piece of research, carried out for my PhD with the supervision and guidance of Prof Mary Horgan, Prof Colm Bergin and Prof John Browne.

I was responsible for applying for and receiving ethical approval from the relevant hospital ethics committees.

For the systematic review, I was responsible for developing search criteria, managing search retrievals, screening articles for possible inclusion, critically appraising relevant articles, and performing the review.

I performed the manual data extraction and data entry of the utilisation data for the micro-costing study. Data from the activity based costing system of CUH was extracted and provided to me in electronic form by Mr Andrew Murphy in CUH finance department.

I performed all statistical analysis reported in this thesis, and I drafted the manuscripts for all included papers.

2 Estimation of the size and age of the HIV population in care in Ireland

2.1 Abstract

Little data are currently available on the number of people accessing HIV care in Ireland and the rate at which the population is growing. Although Ireland has had a case-based reporting system in place since 2002, modelling of the prevalence of HIV infection in Ireland has been hampered historically by a lack of data such as age at diagnosis, CD4 count at diagnosis, proportion of patients on treatment and mortality data. The aim of this chapter is to estimate the number and age breakdown of HIV patients in care in Ireland in 2012, and to generate short-term predictions of the number and age breakdown of HIV patients in care up to the year 2020.

We developed a simple model based on the numbers of cases diagnosed, mortality rates (general and HIV) and loss to follow-up. Four variations of the model were developed using different combinations of estimated age at diagnosis and published HIV mortality rates. The results of all models were compared with observed data. Uncertainty in the model estimates were investigated using one-way sensitivity analysis.

The final selected model estimated that there were 3,820 patients in care in Ireland in 2012, varying from 3,668 to 4,134 on sensitivity analysis. Assuming the number of new cases diagnosed annually remains at current levels the total number of patients in care will increase by 20%, to 4,607, by 2020. The age of patients in care was estimated to be increasing by nearly 0.5 years annually, and the proportion of patients ≥50 years of age will increase from 18% in 2012 to 30% in 2020.

Despite considerable limitations in the data available, the estimates generated provide a useful basis for estimating the likely epidemiological changes to the population of HIV patients in care in the coming years.

2.2 Introduction

The number of new cases of HIV in Ireland has been relatively stable since the early 2000s, with around 300-400 new cases of HIV being diagnosed each year [164]. The prevalence of HIV in the general population is currently estimated to be between 0.2%-0.6% [165,166]. However this is expected to increase in the coming years due to the much improved life-expectancies of HIV patients on HAART. In addition to the expected increase in the volume of patients requiring care, it is also anticipated that the care required will become more complex due to the high rates of multi-morbidity and poly-pharmacy associated with ageing of the HIV population. In the US it has been estimated that the proportion of people over 50 is increasing by 1.5% per year, and that by 2020 over half of HIV cases will be over 50 [167], while in Australia it has been estimated that over 40% of people living with HIV will be over 55 by 2020 [141]. A recent modelling study in the Netherlands estimated that by 2030 73% of HIV patients on treatment will be over 50 and that over 80% of HIV patients on treatment will have at least one, and 28% have at least three, non-communicable chronic diseases [144].

There is widespread concern about the consequences such epidemiological changes will have, not just on HIV services, but also other services such as those providing care for cardiovascular and renal disease [168], cancers [169], organ transplants [170,171] and geriatric medicine [172].

The aim of this chapter is to estimate the number and age breakdown of HIV patients in care in Ireland in 2012, and to generate short-term predictions of the number and age breakdown of HIV patients in care up to the year 2020.

2.3 Methods

2.3.1 Model structure

The number of people in care in any given year is influenced by the number of people in care the previous year, the number of new diagnoses that year, the number of people who are lost-to-follow-up (temporary or permanent), and the number of deaths (both non-HIV and HIV-related mortality).

A simple deterministic model was created in Microsoft Excel® to calculate the number of patients in care at the end of each year in single year age bands, based on the numbers of patients diagnosed in each age band, the number of patients alive and in care at the end of the previous year for the preceding age band, the estimated number of deaths (general mortality and additional mortality due to HIV) and the estimated proportion of patients lost-to-follow-up each year.

Due to limitations in the availability of Irish age at diagnosis and mortality data several variations of the model were created using different estimates for age at diagnosis and mortality.

2.3.1.1 Model 1

This model used published excess HIV mortality rates to estimate the number of HIV related deaths. The calculation used in Model 1 was as follows:

Age band=$_x$

Year=$_i$

Rate of loss-to-follow-up = L

Number of people diagnosed in year *i* in age-group *x*=D_{ix}

Number of people remaining in care at the end of year *i-1* in age group *x-1* who age into age group *x* in year *i* = $N_{(i-1)(x-1)} \times (1\text{-}L) = P_{ix}$

Annual age specific general mortality rate= M

Annual excess mortality rate= E

Number of people in care at the end of year = N

$$\sum_{x=1}^{n} N_{ix} = D_{ix} - \frac{(D_{ix} \times M_{ix}) + (D_{ix} \times E_i)}{2} + P_{ix} - (P_{ix} \times M_{ix}) - (P_{ix} \times E_i)$$

2.3.1.2 Model 2

This model did not estimate the number of HIV deaths using excess mortality rates, instead the number of HIV related deaths per year by age group as estimated by the Global Burden of Disease project were used [173]. The calculation in Model 2 was as follows:

Age band=$_x$

Year=$_i$

Rate of loss-to-follow-up = L

Number of people diagnosed in year *i* in age-group *x*=D_{ix}

Number of people remaining in care at the end of year *i-1* in age group *x-1* who age into age group *x* in year *i* = $N_{(i-1)(x-1)} \times (1\text{-}L) = P_{ix}$

Annual age specific general mortality rate= M

Age specific number of deaths (GBD)= S

Number of people in care at the end of year = N

$$\sum_{x=1}^{n} N_{ix} = D_{ix} - \frac{(D_{ix} \times M_{ix})}{2} + P_{ix} - (P_{ix} \times M_{ix}) - S_{ix}$$

2.3.2 Sources of data

2.3.2.1 Incidence data

Since tests for HIV antibodies became available in 1985, the majority of confirmatory HIV testing in Ireland has been performed by the National Virus Reference Laboratory (NVRL) and from 1985-2002 the NVRL collated all confirmed HIV diagnoses (including confirmatory testing carried out at other laboratories) and reported them to the Department of Health [81,83]. This surveillance was performed on a voluntary basis and it is likely that there were issues with duplicate reporting of cases in this system (the NVRL laboratory information system is a sample-based rather than a person-based system, and samples would frequently have been sent without full names for confidentiality reasons).

In 2001, following a recommendation by the National AIDS Strategy Committee [83] a voluntary case-based reporting system was introduced, administered by the National Disease Surveillance Centre (now the HPSC). This case-based system collected patient level data on the demographic and clinical characteristics of newly diagnosed HIV cases (Figure 2-1).

In 2012 HIV became a statutorily notifiable disease [174]. Named patient data is now reported to the HPSC via the computerised infectious disease reporting system (CIDR), similar to other notifiable diseases.

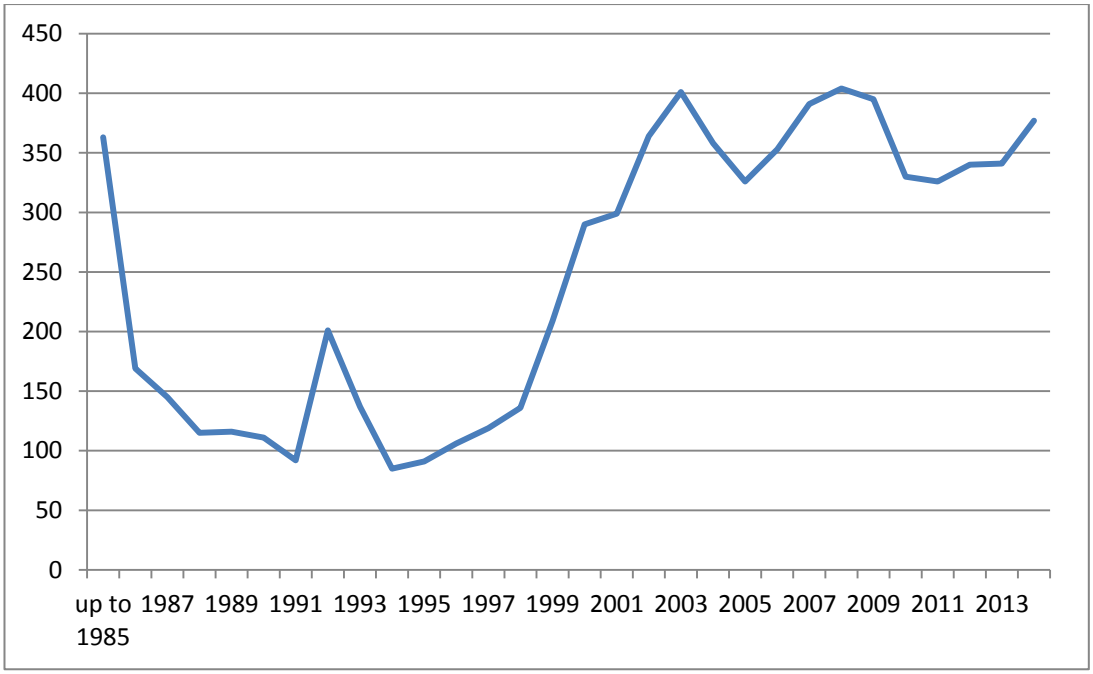


Figure 2-1. Number of new HIV diagnoses in Ireland, 1985-2014. Sources of data 1985-1999 NASC[83], 2000-2014 HPSC annual reports.

2.3.2.2 Age distributions at diagnosis

In order to estimate the age profile of people living with HIV in Ireland it is necessary to have the age distribution, in single years, of newly diagnosed cases. However complete patient level data including age at diagnosis is only available from the HPSC from 2003.

In order to estimate the age distributions of cases diagnosed before 2003 two methods were used.

2.3.2.2.1 Method A

Pre-1992

Although the majority of HIV confirmatory testing has been carried out by the NVRL since tests for HIV became commercially available due to changes in the laboratory

information system, it is not possible for the NVRL to extract data on tests performed before 1992.

The small number of studies reported in the literature from this time were mostly restricted to sub-groups of HIV cases, such as IDUs, and no information was given regarding age at diagnosis [90,175]. One survey of HIV positive patients attending the GUM clinic in St James Hospital between 1989-1991, reported a mean age of participants of 27 years for female IDUs, 29 years for male IDUs and 30 years for MSMs [176]. In this study participants had been diagnosed an average of 2 years. In the absence of other data, the mean and standard deviation of the age at diagnosis was estimated by subtracting the mean number of years since diagnosis from the mean age at the time of the study reported by Comiskey [176].

To take into account the uncertainty in both the mean age at the time of the study and the mean years since diagnosis the mean age at diagnosis was estimated using a Monte Carlo simulation (1,000 iterations). The mean age at diagnosis (and standard deviation) generated by the Monte Carlo simulation were used to estimate the ages of cases diagnosed between 1985 and 1991.

1992-2002

Data was obtained from the NVRL on the age of patients at the time of the first HIV positive test recorded in their laboratory system between 1992 and 2002. The NVRL extracted all positive HIV tests 1992-2002 and this list was de-duplicated keeping only first positive sample by date. All positives in babies up to 9 months old were also removed as the positive result may have been due to maternal antibodies.

Weak HIV positives were manually checked for subsequent confirmed positive HIV result. Results with no information on age were excluded.

The mean age and standard deviation of this NVRL data was used to construct estimates of the ages of diagnosed cases 1992-2002 based on the total number of new diagnoses notified [83].

One important limitation that should be mentioned is that as it was not possible to extract data on samples which tested HIV positive before 1992, it is likely that some of the patients with positive samples included in this extraction would have been diagnosed previously, resulting in an over estimation of the mean age at diagnosis.

2003-2014

Data on the number of cases in single year age bands were obtained from HPSC for cases diagnosed 2003-2014.

2014-2020

The number and age-breakdown of new cases each year 2015-2020 was assumed to be an average of the number of cases notified in the previous five years (2010-2014).

2.3.2.2.2 Method B

Due to concerns about the accuracy of these estimated age distributions, particularly as the age at diagnosis between 1992 and 2002 data was likely to be overestimated, time series analysis of the mean age at diagnosis 2003-2014 was used to predict the mean age of diagnosis each year from 1985 to 2020 (Figure 2-2). The predicted age in combination with the average standard deviation of ages of

cases notified to the HPSC 2003-2014 (mean of the standard deviation was 10.68, range 9.13-13.89) were used to construct age distributions of cases in single-year age groups for years up to 2002.

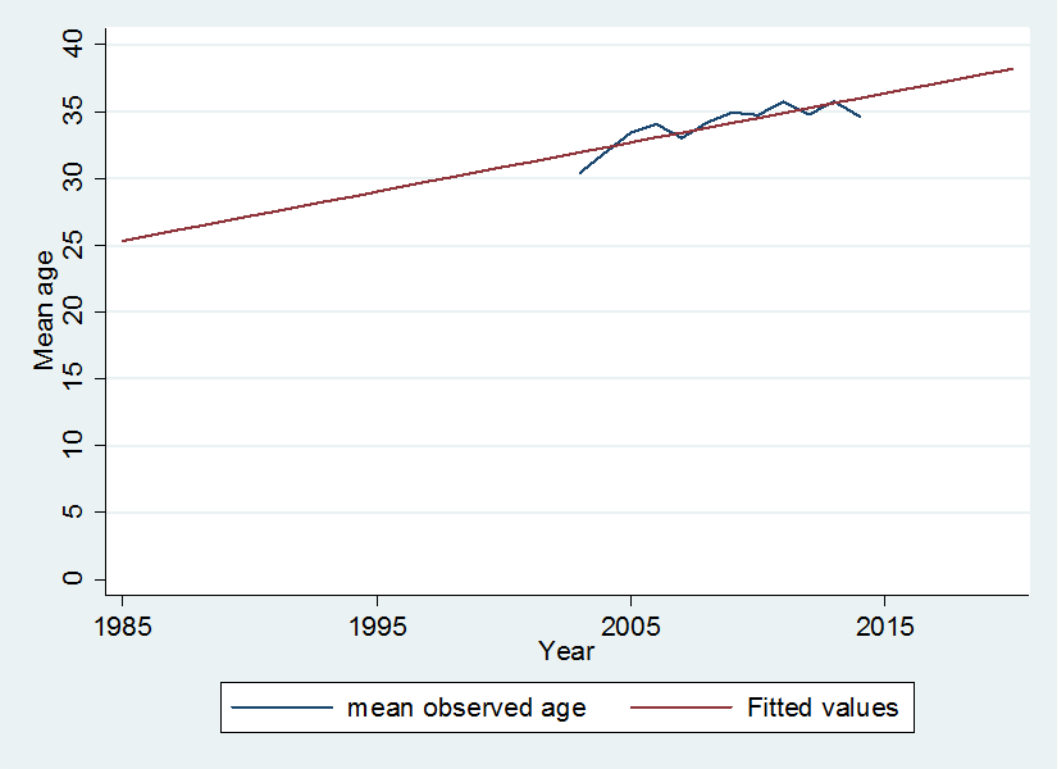


Figure 2-2. Observed and predicted mean age at diagnoses 1985-2020, predicted ages based on time series analysis.

2.3.2.3 Loss-to-follow-up

There is no routine data available in Ireland on loss-to-follow-up. In the UK, it was found that approximately 10% of patients who attend in a given year do not attend care the following year [79], on further investigation 5% of these were considered lost-to-follow-up, with 4% subsequently attending care in a subsequent year (intermittent attenders), while less than 2% had died. A similar annual loss-to-follow up was also reported by EuroSIDA, a multi-centre prospective observational study of HIV patients in Europe [177].

No national data is available in Ireland on loss-to-follow up. In order to estimate if 5% would be a reasonable estimate of loss-to-follow-up in Ireland data on the number of patients attending each year was extracted from a clinical database of viral load results maintained in CUH. Between 1997, when the unit was established, and 2012 the proportion of patients who attended in a given year (as indicated by the presence of at least one recorded viral load result) but who did not attend care the following year was 12% (Table 2-1). On average 7% of patients who attended in a given year had no further viral loads recorded (i.e. were lost-to-follow-up in CUH) while 5% re-attended in a subsequent year. Although the 7% of patients who no longer attended CUH is higher than the estimates of loss-to-follow-up reported in the UK [79] and EuroSIDA [177] as these data were from a single centre it was not possible to differentiate between patients who transferred to another centre (i.e. remained in care) and those who dropped completely out of care (either permanently or temporarily). Data from a study in SJH found a cumulative loss to follow up (failure to attend the clinic for more than a year) of 11% over the period 2007-2014 (personal communication Dr Sarah O'Connell, 11/02/2016).

2.3.2.4 Mortality data

Data on the number of deaths due to HIV/AIDS in Ireland are not thought to be very reliable. Particularly in the early years of the epidemic, when no effective treatment was available the number of deaths attributed to HIV/AIDS is thought to be underestimated due to the considerable stigma attached to a HIV diagnosis.

Table 2-1. Loss-to-follow up in CUH, based on clinic viral load (VL) database.

Year	Number of patients with at least one VL	Number of patients with at least one VL recorded the following year	% with a VL recorded the following year	% with subsequent VLs recorded	% no subsequent VLs recorded
1997	13	13	100%	0%	0%
1998	42	37	88%	5%	7%
1999	61	49	80%	15%	5%
2000	76	56	74%	25%	1%
2001	91	67	74%	5%	21%
2002	144	123	85%	6%	9%
2003	178	156	88%	3%	9%
2004	187	167	89%	2%	9%
2005	214	193	90%	2%	7%
2006	244	216	89%	2%	9%
2007	261	242	93%	2%	5%
2008	312	284	91%	2%	7%
2009	340	322	95%	1%	4%
2010	367	330	90%	1%	9%
2011	375	346	92%	0%	8%
2012	388	-	-	-	-
Average			88%	5%	7%

2.3.2.4.1 Routine national mortality data

Routine mortality data including cause of death is collated from death certificates by the Central Statistics Office (CSO) in Ireland. Data on age-specific general mortality rates in 5-year age groups, 1980-2013 were downloaded from the Health Well website [178].

HIV/AIDS mortality

Deaths due to HIV/AIDS have only been specifically coded as an underlying cause of death since the introduction of ICD-10 coding by the CSO in 2007. Prior to that, HIV/AIDS deaths were coded to an umbrella code (ICD-9 279.8 “Other specified disorders involving the immune system”) not specific to HIV/AIDS and which may contain non-HIV/AIDS deaths (CSO personal communication, 24/11/2015).

Table 2-2. Number of deaths with an underlying code of ICD9 279.8 or ICD10 B20-B24 (CSO), and number of deaths in people with HIV/AIDS reported to the HSPC

	Routine mortality data		Deaths in people with HIV/AIDS	
Year	**Number of deaths**	**Code and source**	**Number of deaths**	**Notes**
1985	1	Underlying cause of death ICD9 279.8 (other specified disorders involving the immune mechanism) Source, personal communication CSO, 24/11/2015)	4	Deaths reported to HPSC in patients with HIV/AIDS, death may or may not be HIV/AIDS related. Personal communication HPSC 10/12/2015. * deaths at time of diagnosis only reported
1986	1		5	
1987	2		13	
1988	6		9	
1989	9		22	
1990	8		18	
1991	16		26	
1992	28		44	
1993	41		38	
1994	29		39	
1995	51		50	
1996	33		33	
1997	15		11	
1998	13		11	
1999	18		17	
2000	5		10	
2001	10		13	
2002	11		10	
2003	17		5	
2004	15		27	
2005	8		25	
2006	7		15	
2007	15	Underlying cause of death ICD10 B20-B24, HIV/AIDS [102-109]	14	
2008	14		5	
2009	13		8	
2010	13		6	
2011	14		15	
2012	12		1*	
2013	6		3*	
2014	9		1*	

(Note: for 2001-2006, deaths coded as ICD9 279.8 were reported in the CSO Annual Vital Statistics Reports as deaths due to HIV/AIDS)

2.3.2.4.2 Surveillance data

As part of the voluntary HIV/AIDS surveillance system the Department of Health collated the number of HIV/AIDS cases and deaths from 1982 until this function was

transferred to the HPSC in 2000 [83]. In the voluntary case-based reporting system which operated between 2001 and 2011, clinicians were also requested to report the details of deaths in their HIV/AIDS patients.

Up to 2011 505 deaths (8% of all notifications, including 12 deaths with an unknown year of death) in people with HIV had been reported to HPSC (Table 2-2), however not all these deaths were necessarily HIV-related (Dr Kate O'Donnell, personal communication 22/04/2015). Since 2012 only information on deaths reported at the time of diagnosis has been collected by the HPSC [82].

2.3.2.4.3 Longitudinal studies

Many longitudinal studies have reported mortality rates in HIV positive populations in developed countries. These mortality rates have dropped dramatically since the widespread introduction of HAART from pre-HAART mortality ranging from 50-100 deaths per 1,000 person years [179-182] to around 10-25 deaths per 1,000 person years in the HAART era [179,181-187].

As no data on the rate of excess mortality in the Irish HIV population are available, the excess mortality rates reported by a large multi-national collaboration of HIV seroconverter cohorts (CASCADE), mainly located in European countries [188], were applied to the Irish HIV population (Table 2-3). This study was chosen as it reported excess mortality rates with 95% confidence intervals for a range of years covering pre, early and late HAART eras.

Table 2-3. Excess mortality rates reported by CASCADE [188]

	Excess mortality rate (per 1,000 py)	95% CI	Years applied
Pre-1996	40.8	38.5-43.0	All years pre 1996
1996-1997	31.4	28.5-34.2	1996-1997
1998-1999	11.9	10.2-13.5	1998-1999
2000-2001	9.5	8.1-10.9	2000-2001
2002-2003	8.5	7.1-9.9	2002-2003
2004-2006	6.1	4.8-7.4	2004-2020
Total	20.7	19.9-21.6	

To assess the likely generalizability of these excess mortality rates to the Irish context the age structure of the CASCADE participants were compared to the estimated age distributions of the Irish notification data (see Figure 2-3). The age composition of the cohort was reasonably similar to the age structure of notified cases in Ireland, however, on χ^2 testing the proportions in each age group (as estimated by both method A and B above) were all significantly different than the CASCADE participants for the equivalent time periods. One possible explanation is that as the CASCADE collaboration only included seroconverter cohorts, the patients included in these cohorts would tend to be diagnosed earlier (therefore younger) compared to the general HIV population.

In addition, a greater proportion of Irish notifications were females compared to the proportion of females in the CASCADE cohorts (37% female between 2000-2014 v 22% female in CASCADE). There were also some differences in risk groups, with Irish notification data having comparatively higher proportions of IDUs and a lower proportion of MSMs [83,188,189].

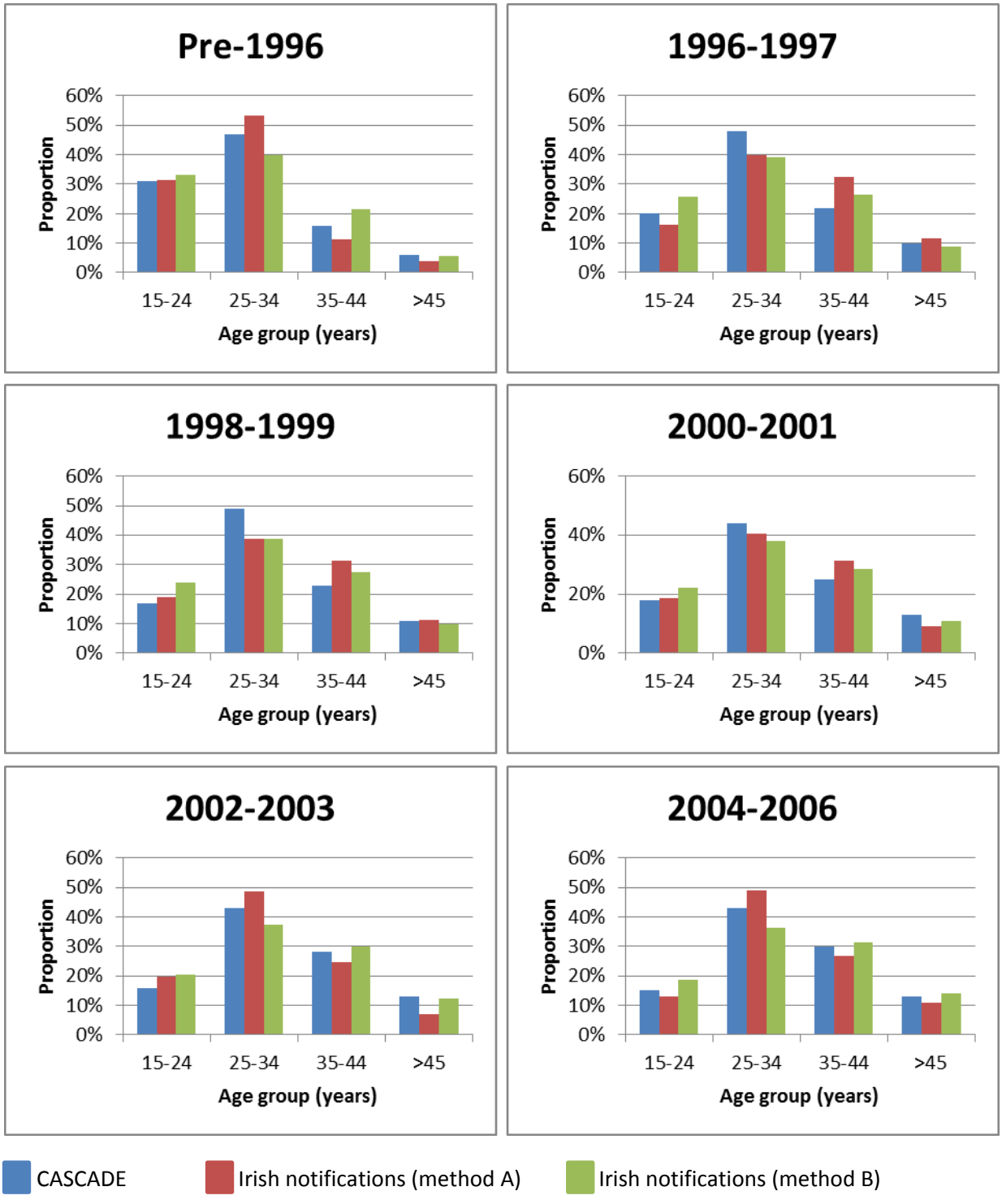


Figure 2-3. Comparison of age distribution of CASCADE collaboration and estimated Irish notification data

2.3.2.4.4 Modelled estimates

The Global Burden of Diseases, Injuries and Risk Factors Study (GBD) is an international collaboration, led by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington. Its purpose is to systematically quantify levels and trends in mortality, disability, disease burden, life expectancy and risk factors at global, regional and national levels. GBD (2013) HIV mortality and incidence estimates were based primarily on a modified version of the UNAIDS Spectrum model [190], which is a compartmental HIV progression model (an illustration of which is shown in Figure 2-4). For countries with concentrated epidemics the HIV incidence data required by the Spectrum model have historically been generated based on data on specific high risk groups (the percentage of the population and the prevalence of HIV in each group). These data, however, are often lacking and an alternative is to track the epidemic through deaths reported in the vital registration systems. Vital registration data often underestimate the number of HIV deaths as deaths may be misclassified or assigned to immediate or intermediate causes of death (i.e. garbage codes) rather than the underlying cause of death.

Attempting to address these limitations, the GBD study generates adjusted HIV mortality estimates by redistributing the number of deaths coded under “garbage codes” (some of the redistribution is proportional, some is based on statistical methods, and some is based on evidence from the literature [190]) and correcting for misclassification (using a method developed by Birnbaum and colleagues [191]) and uses these estimates to calibrate their modified Spectrum model [190].

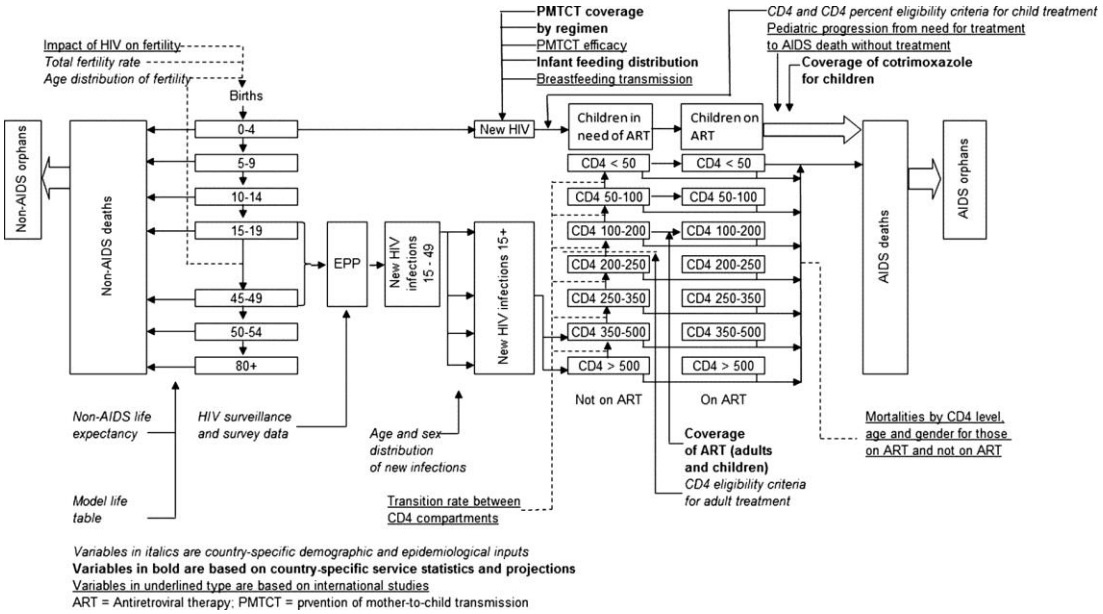


Figure 2-4. Diagram of Spectrum/Estimation and Projection Package (EPP) model [192].

The estimated cumulative number of HIV deaths in Ireland produced by this methodology was around 470 by 2013 (estimated range 338-646)[173] (Figure 2-5). GBD estimated the number of HIV/AIDS deaths in Ireland was between 12 and 25 in 2013 [190] compared to 3 deaths reported to the HPSC [82] and 6 deaths reported by the CSO [193].

For 2014-2020, the average of the GBD estimated number of deaths per year for the preceding 5 years (2009-2013) was used.

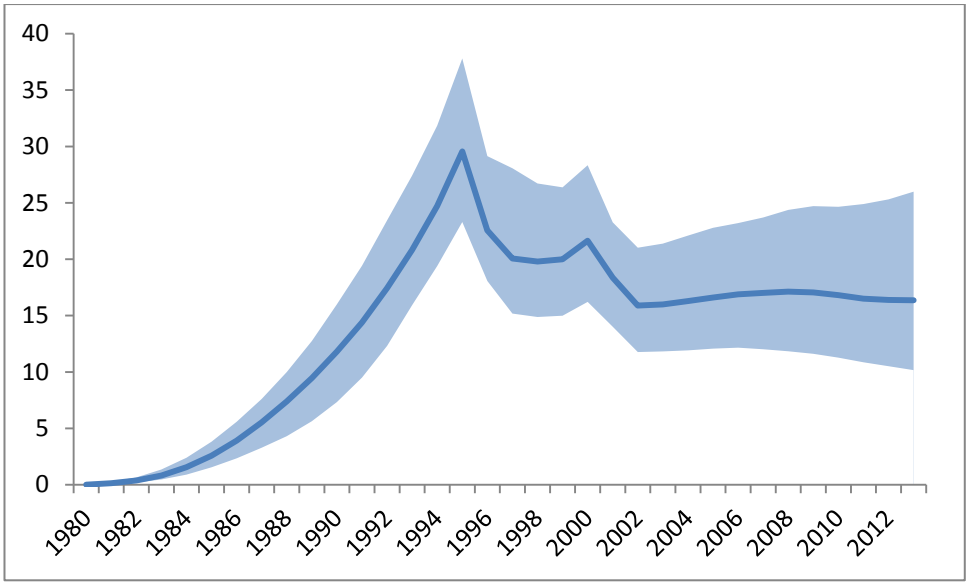


Figure 2-5. GBD estimated number (range) of HIV/AIDS deaths per year 1980-2013 ([173] data downloaded 21/4/2015)

2.3.3 Model validation

There is currently no routinely collected data on the number of patients in care. A prevalence study was carried out in 2009/2010 which identified that there were 3,254 patients accessing care at that time [85]. The total number and age distribution of patients in care in 2009/2010 was compared to the estimated total numbers and age distributions generated by the various models. χ^2 tests were used to test the significance of differences between the proportions of patients in each age group as estimated by the various models to the observed data.

2.3.4 Sensitivity analysis

Uncertainty in the model estimates were investigated using one-way sensitivity analysis varying the mean age at diagnosis and proportion of patients lost-to-follow-up annually, based on the 95% confidence intervals of source data. The annual number of deaths was varied based on the difference between the total

number of deaths in Ireland per year as estimated by the GBD and UNAIDS (spectrum) estimates.

2.4 Results

2.4.1 Model 1a

Model 1a: the number of deaths per year in each age group estimated using published excess mortality rates [188]. The age distributions of cases each year was estimated using method A (see section 2.3.2.2.1 above), Figure 2-6. The 95% confidence intervals of the published excess mortality rates [188] were used to generate alternative estimates given low/high excess mortality (Table 2-4).

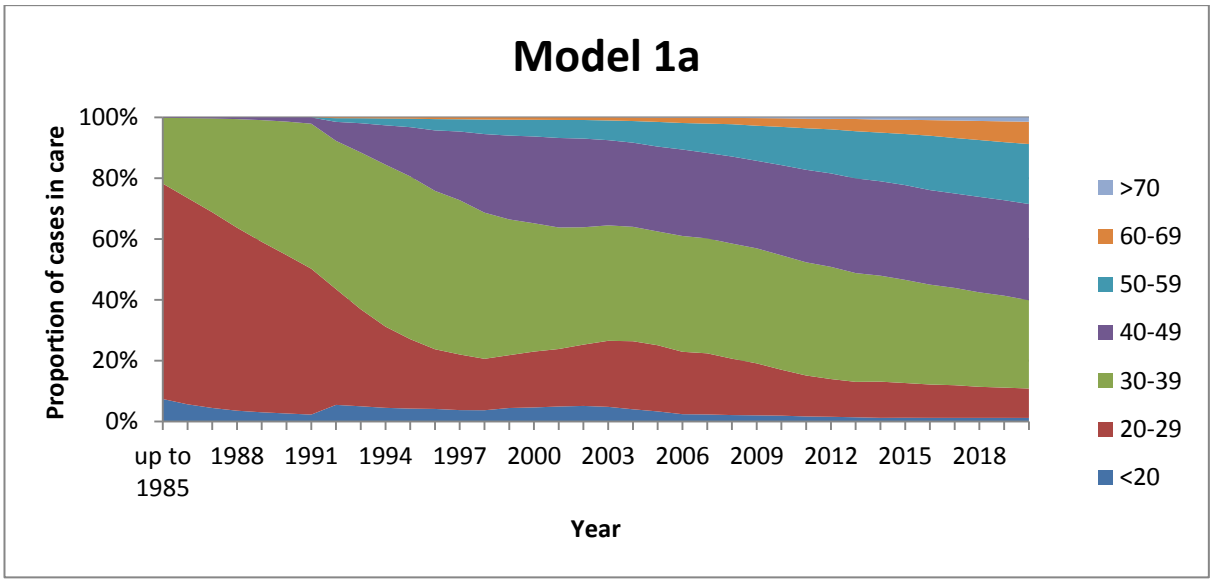


Figure 2-6. Estimated age distribution of HIV cases in care, 1985-2020 model 1a, mean mortality estimate

Table 2-4. Estimated total number of people in care, by age group, 2012 and 2020, model 1a

Age group	2012	2012 (low mortality)	2012 (high mortality)	2020	2020 (low mortality)	2020 (high mortality)
< 20	59	59	59	54	54	53
20-29	477	480	474	449	451	447
30-39	1,419	1,431	1,408	1,347	1,359	1,335
40-49	1,181	1,196	1,167	1,469	1,490	1,449
50-59	558	568	547	915	933	898
60-69	132	134	130	327	349	332
70+	18	18	18	79	67	64
Total	3,845	3,887	3,803	4,641	4,703	4,580

2.4.2 Model 1b

Model 1b: number of deaths per year in each age group estimated using published excess mortality rates [188]. The age distributions of cases each year was estimated using method B (see section 2.3.2.2.2 above) Figure 2-7. The 95% confidence intervals of the published excess mortality rates [188] were used to generate alternative estimates given low/high excess mortality (Table 2-5).

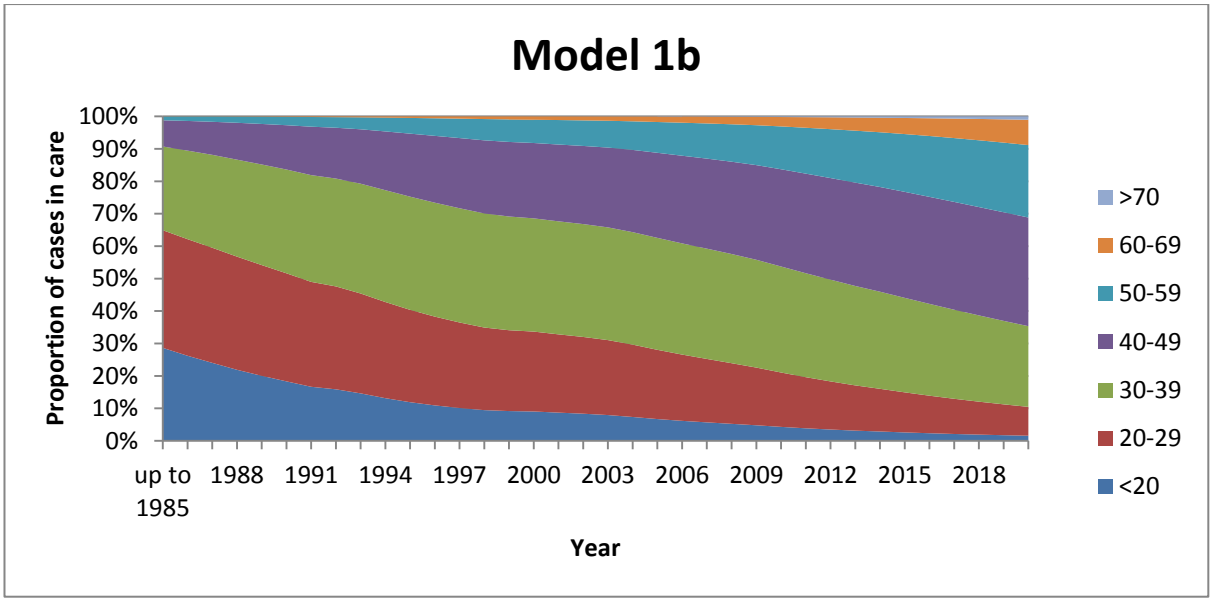


Figure 2-7. Estimated age distribution of cases in care 1985-2020, model 1b, mean mortality estimate

Table 2-5. Estimated total number of people in care, by age group, 2012 and 2020, model 1b

Age group	2012	2012 (low mortality)	2012 (high mortality)	2020	2020 (low mortality)	2020 (high mortality)
< 20	134	135	133	73	73	72
20-29	570	574	566	413	416	410
30-39	1,206	1,217	1,195	1,154	1,166	1,143
40-49	1,204	1,218	1,190	1,555	1,575	1,535
50-59	580	589	571	1,036	1,054	1,019
60-69	140	143	137	362	370	354
70+	11	11	11	48	50	47
Total	3,844	3,887	3,803	4,641	4,704	4,581

2.4.3 Model 2a

Model 2a: number of deaths per year in each age group as estimated by GBD [173]. The age distributions of cases each year was estimated using method A (see section 2.3.2.2.1 above), Figure 2-8. The 95% confidence intervals of the GBD estimates were used to generate alternative estimates given low/high estimated number of deaths (Table 2-6).

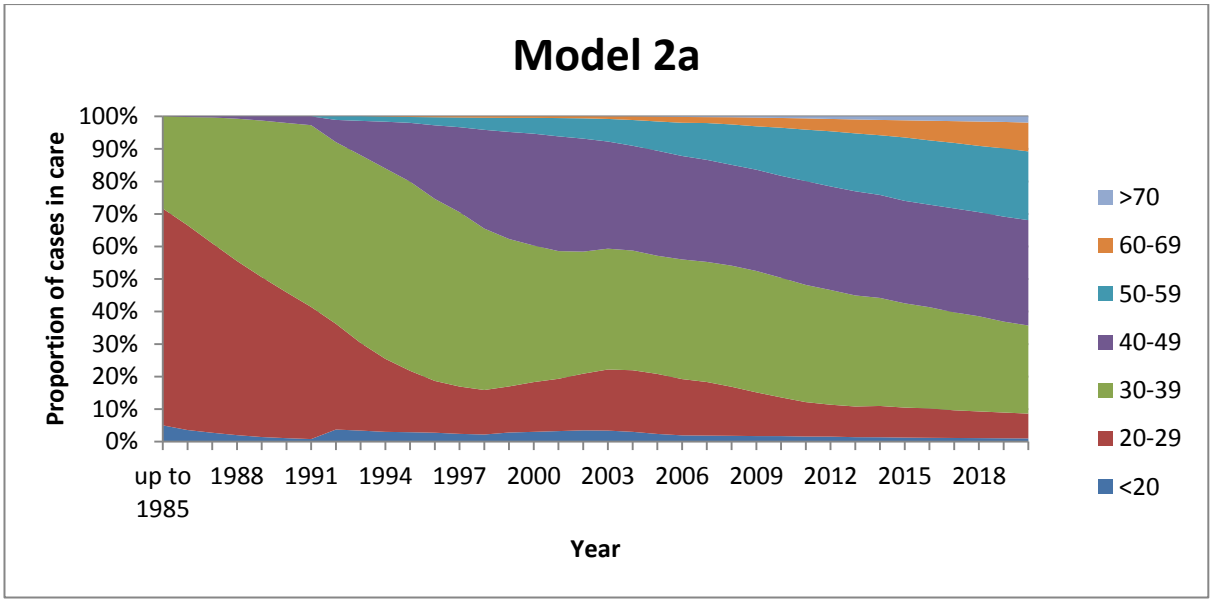


Figure 2-8. Estimated age distribution of cases in care 1985-2020, model 2a, mean mortality estimate

Table 2-6. Estimated total number of people in care, by age group, 2012 and 2020, model 2a

Age group	2012	2012 (low mortality)	2012 (high mortality)	2020	2020 (low mortality)	2020 (high mortality)
< 20	61	61	61	47	47	47
20-29	388	391	385	364	367	359
30-39	1,396	1,410	1,370	1,294	1,308	1,274
40-49	1,260	1,286	1,222	1,547	1,580	1,503
50-59	671	701	631	1,009	1,045	963
60-69	150	162	123	423	445	384
70+	31	34	28	91	101	77
Total	3,957	4,045	3,820	4,775	4,893	4,607

2.4.4 Model 2b

Model 2b: number of deaths per year in each age group as estimated by GBD [173]. The age distributions of cases each year was estimated using method B (see section 2.3.2.2.2 above), Figure 2-9. The 95% confidence intervals of the GBD estimates were used to generate alternative estimates given low/high estimated deaths (Table 2-7).

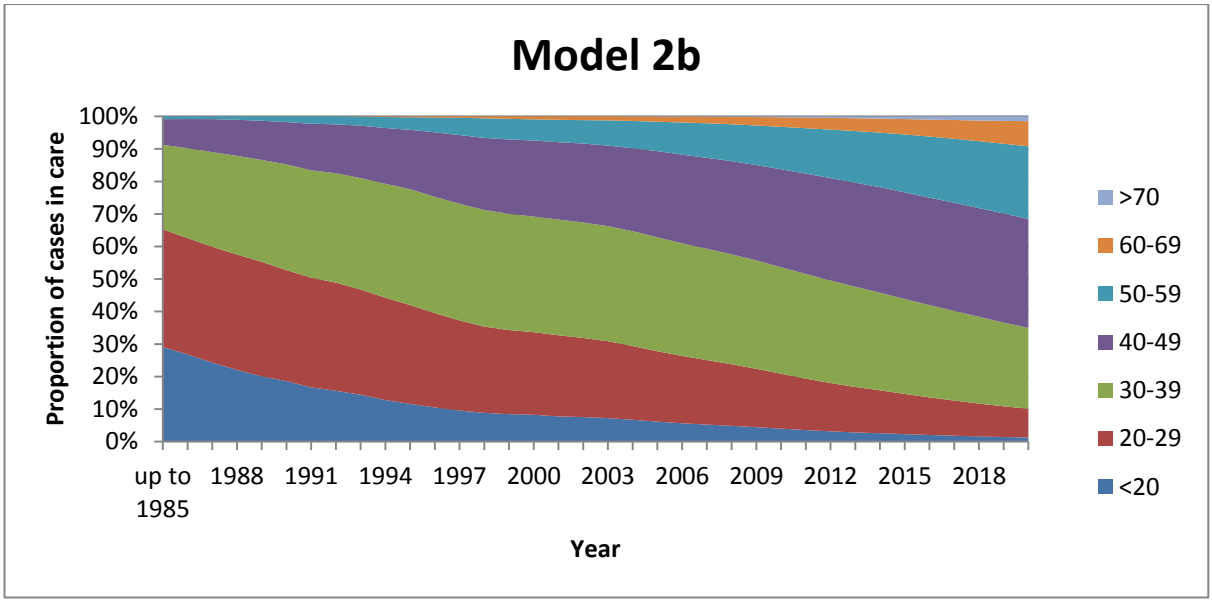


Figure 2-9. Age distribution of cases in care 1985-2020, model 2b, mean mortality estimate

Table 2-7. Estimated total number of people in care, by age group, 2012 and 2020, model 2b

Age group	2012	2012 (low mortality)	2012 (high mortality)	2020	2020 (low mortality)	2020 (high mortality)
< 20	124	124	124	60	60	60
20-29	583	587	576	421	423	417
30-39	1,237	1,252	1,211	1,183	1,195	1,158
40-49	1,235	1,262	1,197	1,593	1,622	1,551
50-59	585	611	542	1,065	1,101	1,018
60-69	141	159	120	367	390	333
70+	18	20	13	70	74	57
Total	3,923	4,015	3,783	4,759	4,865	4,594

2.4.5 Comparison of model results for 2012

The use of GBD estimates of the number of deaths (i.e. models 2a and 2b) resulted in a slightly higher estimated number of patients in 2012 compared to the models using published excess mortality rates (models 1a and 1b), see Table 2-8. While the use of data-based age estimates (method A) rather than predicted mean age estimates to reconstruct the age breakdown of diagnosed cases (method B) resulted in a more pronounced peak of cases in the 30-39 year age group in 2012 (Figure 2-10).

Table 2-8. Comparison of estimated number of patients attending care in 2012, produced by models 1a, 1b, 2a and 2b.

Age group	Model 1a (high-low mortality)	Model 1b (high-low mortality)	Model 2a (high-low mortality)	Model 2b (high-low mortality)
< 20	59 (59-59)	134 (133-135)	61 (61-61)	124 (124-124)
20-29	477 (474-480)	570 (566-574)	388 (385-391)	583 (576-87)
30-39	1,419 (1,408-1,431)	1,206 (1,195-1,217)	1,396 (1,370-1,410)	1,237 (1,211-1,252)
40-49	1,181 (1,167-1,196)	1,204 (1,190-1,218)	1,260 (1,222-1,286)	1,235 (1,197-1,262)
50-59	558 (547-568)	580 (571-589)	671 (631-701)	585 (542-611)
60-69	132 (130-134)	140 (137-143)	150 (123-162)	141 (120-159)
70+	18 (18-18)	11 (11-11)	31 (28-34	18 (13-20)
Total	3,845 (3,803-3,887)	3,844 (3,803-3,887)	3,957 (3,820-4,045)	3,923 (3,783-4,015)

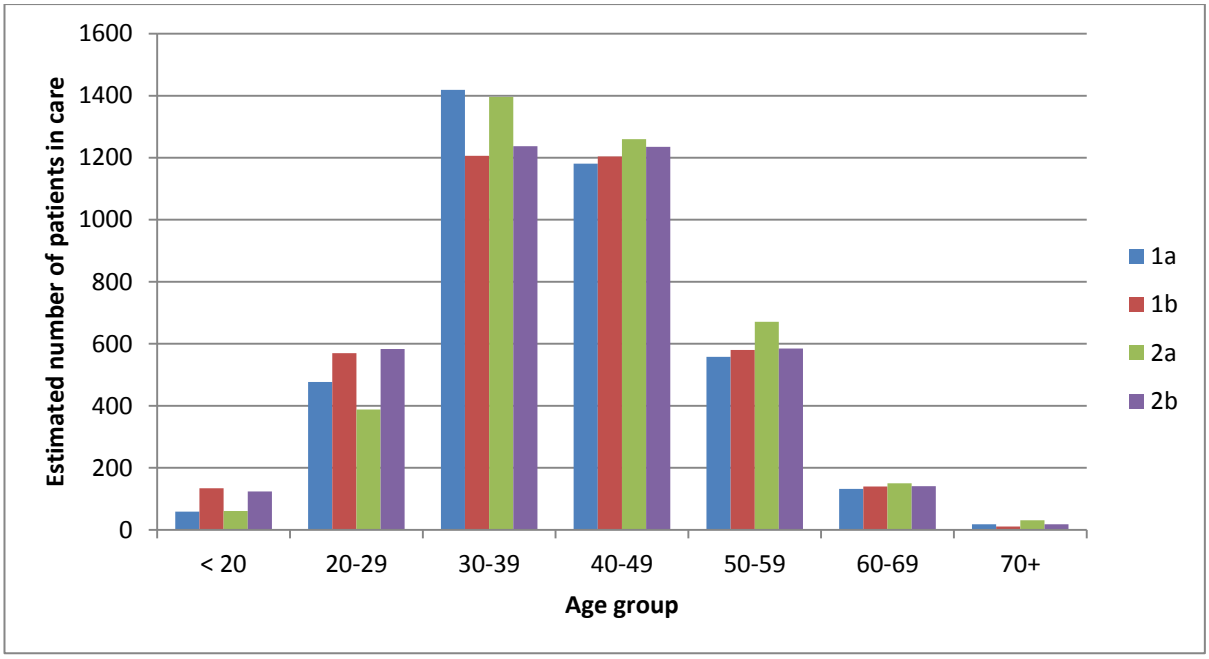


Figure 2-10. Comparison of estimated age breakdown of cases in care 2012, model 1a, 1b 2a and 2b.

2.4.6 Model Validation

The only available data on the number and age profile of patients attending HIV care in care Ireland is from a national prevalence study carried out in 2009/2010 [85]. The average age distribution for 2009 and 2010 as estimated by the various models were tested against the observed age distribution (Table 2-9) and the age distributions were all found to be significantly different, apart from model 2a (high mortality). The total number of patients in care in 2009/2010 as estimated by this model (the final model) was 3,510 (average of 2009 and 2010) compared to 3,254 patients identified in the prevalence study carried out by Tuite et al. [85]. While this appears to be quite a large difference, 8% higher than the number of patients observed in the prevalence study, that study did not include private patients.

Table 2-9. Comparison of averaged 2009 and 2010 model results to observed data

Age group (years)	Observed	1a	1a low mortality	1a high mortality	1b	1b low mortality	1b high mortality	2a	2a low mortality	2a high mortality	2b	2b low mortality	2b high mortality
15-25	4.72%	6.48%	6.45%	6.51%	11.32%	11.27%	11.36%	5.05%	4.96%	5.21%	11.26%	11.00%	11.54%
26-35	30.10%	33.46%	33.33%	33.58%	28.33%	28.26%	28.40%	30.62%	30.14%	31.21%	28.46%	28.07%	28.87%
36-45	39.36%	35.26%	35.25%	35.26%	34.29%	34.28%	34.29%	35.93%	35.77%	36.26%	34.38%	34.15%	34.74%
46-55	20.31%	18.90%	19.04%	18.76%	19.79%	19.85%	19.73%	21.85%	22.16%	21.54%	19.65%	19.92%	19.23%
56-65	4.32%	4.99%	5.01%	4.96%	5.53%	5.57%	5.48%	5.36%	5.65%	4.75%	5.36%	5.85%	4.96%
66+	1.17%	0.91%	0.92%	0.91%	0.75%	0.76%	0.74%	1.19%	1.31%	1.02%	0.90%	1.01%	0.65%
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.041	0.009	0.159	<0.001	<0.001	<0.001

(Source of observed data personal communication Dr Helen Tuite, 6/12/2015)

2.4.7 Final model results

The age distribution of cases in care each year as estimated by the final model selected is shown in Figure 2-11. The model estimates the total number of people in care has been increasing by 3%-4% each year between 2010-2014, and that this number will continue to increase by about 2% each year from 2015-2020 (Figure 2-12). The average age of patients in care has increased by an average of 0.49 years annually over the last 10 years (2005-2014) (Figure 2-13), and the proportion of patients >50 years is estimated to increase from 18% in 2012 to 30% in 2020.

The proportion of patients aged ≥50 years in Ireland appears lower than that reported by some other developed countries (Figure 2-14). The differences between countries can be explained by variations in the definitions (e.g. patients diagnosed vs patients in care) and methodologies (surveys vs modelling) used as well as by underlying differences in the age structure of the population and HIV epidemiology. However, it does appear that the rate at which the proportion of older patients is increasing is consistent across countries.

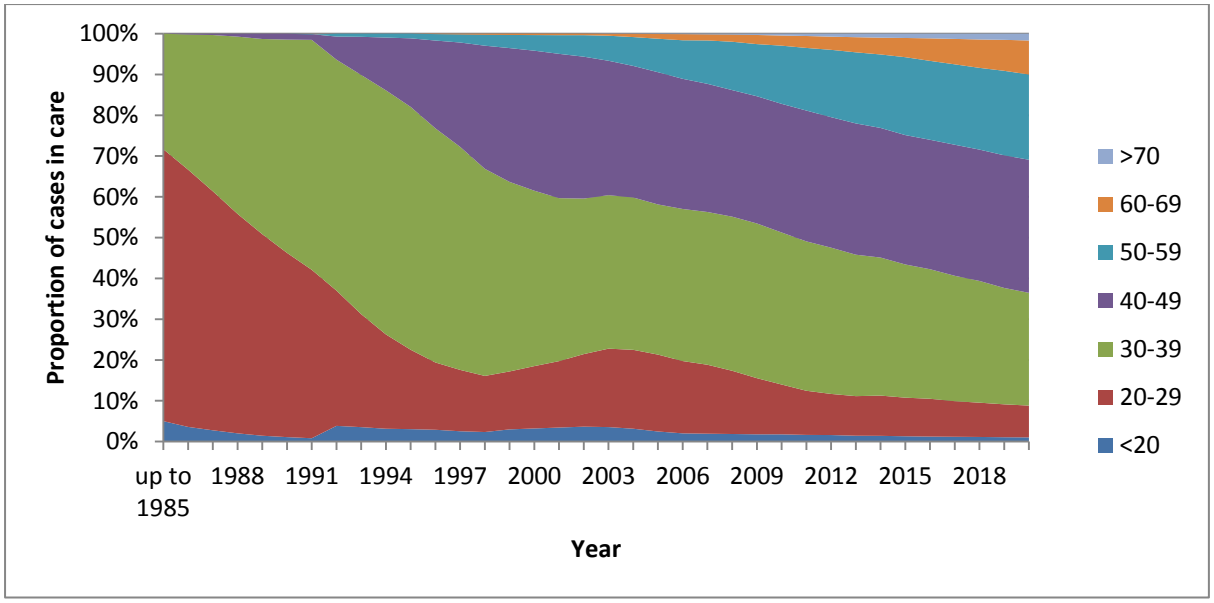


Figure 2-11. Age distribution of patients in care, final model

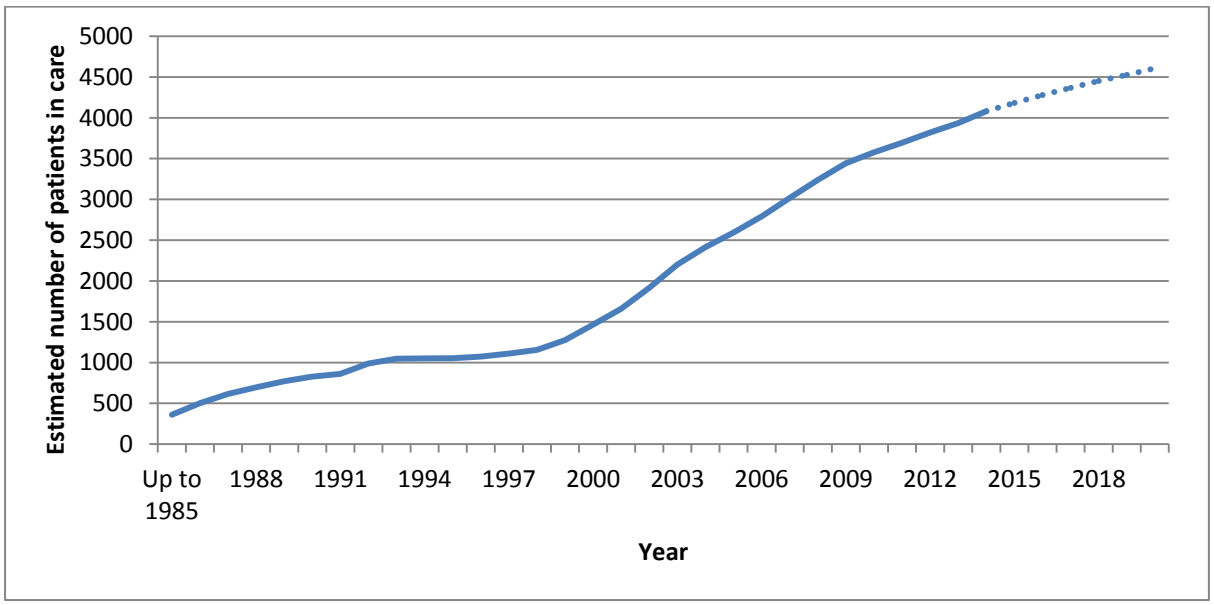


Figure 2-12. Estimated total number of patients in care 1985-2020, final model

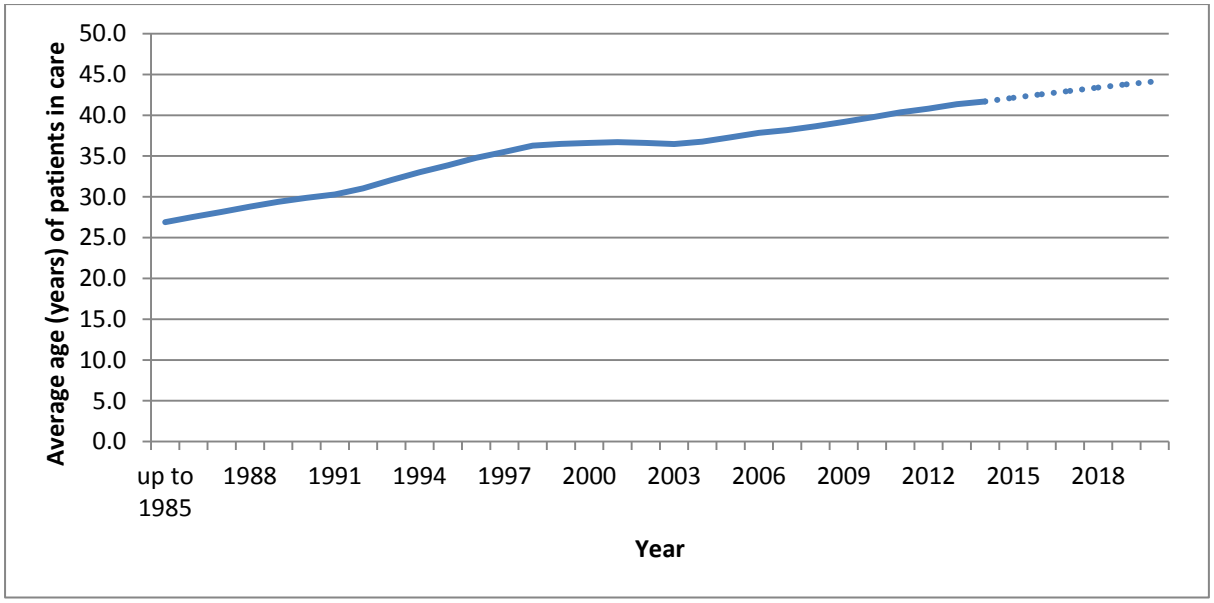


Figure 2-13. Estimated average age of patients in care by year, final model

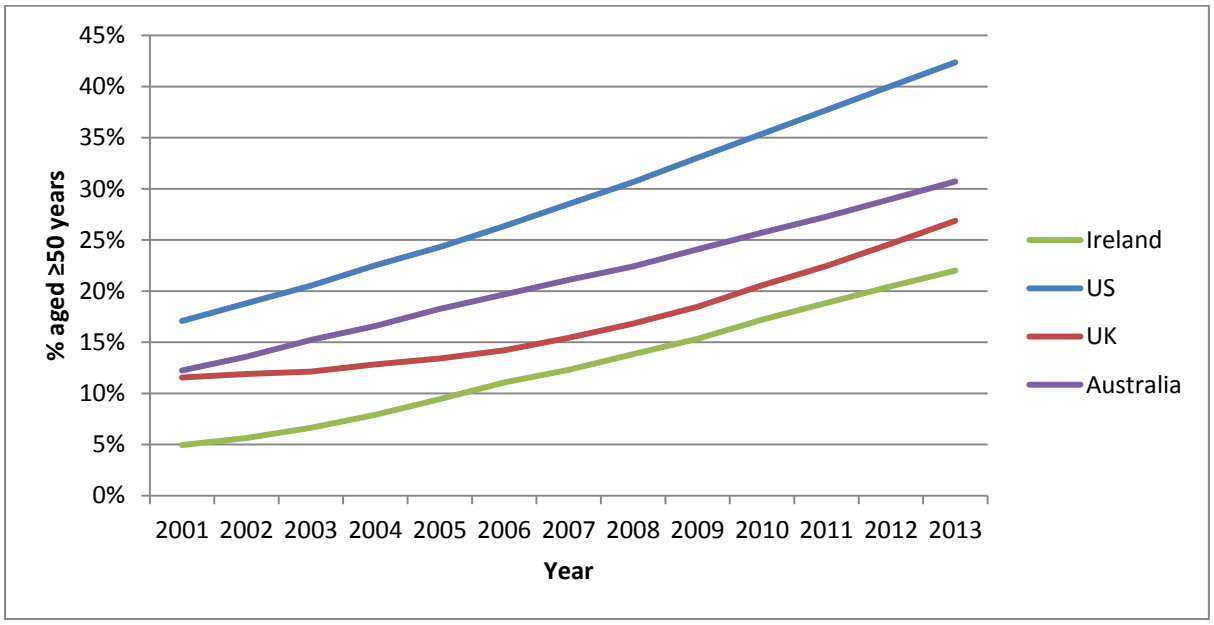


Figure 2-14. Proportion of people living with diagnosed HIV (US and Australia) or in care for HIV (Ireland and UK) aged ≥50 years (Australia ≥55 years), 2001-2013 (Sources of data: US, CDC surveillance reports for years 2004, 2008, 2009, 2011, and 2013 [194]; UK, HIV in the UK reports for years 2011, 2013 and 2014 available at https://www.gov.uk/government/statistics/hiv-in-the-united-kingdom ; Australia [195].)

2.4.8 Sensitivity Analysis

One way sensitivity analysis of the final model was performed, varying the mean age at diagnosis (pre-2003 only), loss-to-follow-up and annual number of deaths.

Age at diagnosis

The lower and upper bounds of the 95% confidence intervals of the mean age at diagnosis for the years pre-1991 (based on the results of the Monte Carlo simulation) and 1992-2002 (based on NVRL first positive samples) were used to construct alternative age distributions of notified cases for those years.

Loss-to-follow-up

Loss-to-follow-up was varied based on the 95% confidence intervals (4%-6%) of the rate of loss-to-follow up, calculated based on data reported by Rice et al. (2011) [79].

Number of deaths

The estimated number of deaths used in the base case model was the higher bound of the GBD estimates. The GBD methodology tends to result in a lower number of deaths compared to UNAIDS (Spectrum) estimates [190]. For sensitivity analysis the total estimated number of AIDS-related deaths in Ireland (1990-2014) as estimated by UNAIDS [26] was compared to the total number of HIV/AIDS deaths in Ireland as estimated by the GBD project [173] (Figure 2-15). The proportional difference between the upper bound of the GBD estimates and the mean UNAIDS estimate were calculated for each year that estimates from both sources were available (1990-2013), and the number of deaths in all age groups were multiplied by that proportion. The 1990 proportional difference was applied for years before 1990 and the proportional difference in 2013 was applied to years after 2013.

The results of all the sensitivity analyses performed are shown in Table 2-10. The results were most sensitive to variation in the estimate of loss-to-follow up, with a variation of ±1% resulting in a difference of ±8% from base case estimates in 2012. The mean age and proportion ≥50 years of age varied relatively little on sensitivity analysis.

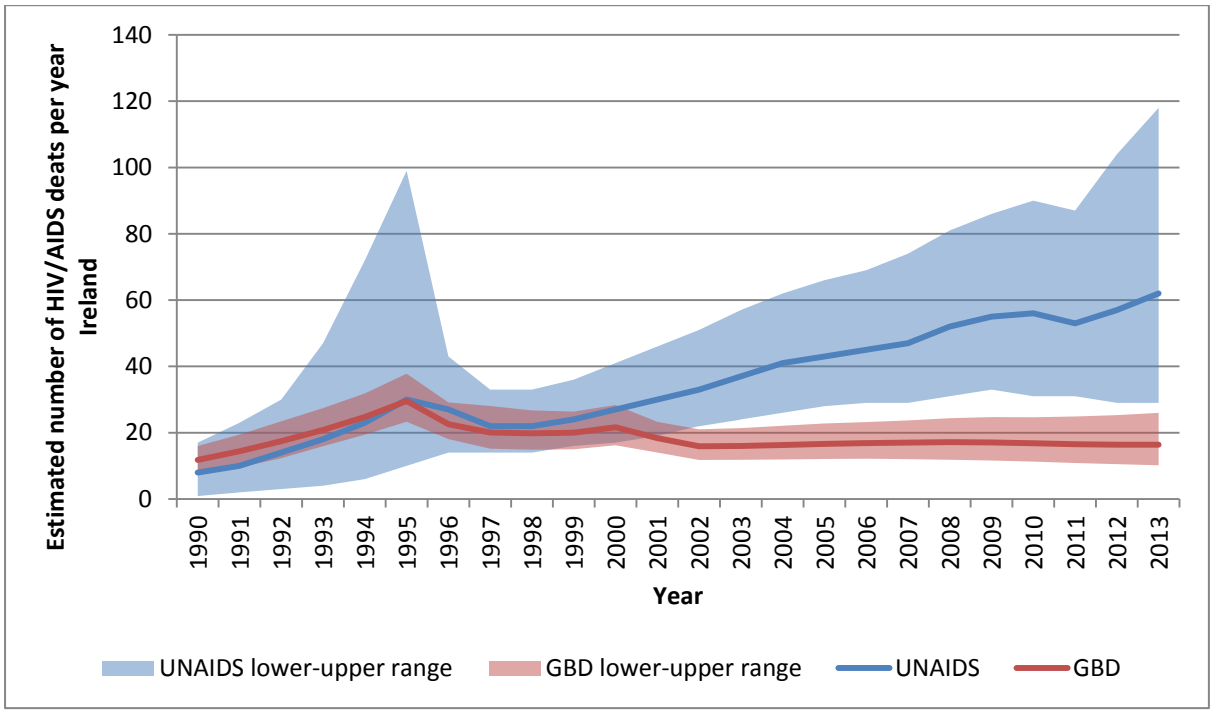


Figure 2-15. Comparison of GBD and UNAIDS (spectrum) estimates of number of HIV/AIDS deaths in Ireland 1990-2013 (UNAIDS data downloaded 8/12/2015)

Table 2-10. Results of one-way sensitivity analysis

	Total number of patients in care 2009/2010	Mean age of patients 2009/2010	% patients ages ≥50 years 2009/2010	Total number of patients 2012	Mean age of patients 2012	% patients ages ≥50 years 2012	Total number of patients 2020	Mean age of patients 2020	% patients ages ≥50 years 2020
Base case	3,510	39.5	16%	3,820	40.8	20%	4,607	44.1	31%
Lower estimate of mean age pre 2003	3,507	39.1	15%	3,811	40.5	19%	4,605	44.0	30%
Higher estimate of mean age pre 2003	3,516	39.8	18%	3,824	41.1	22%	4,609	44.3	31%
Lower estimate of annual loss-to-follow-up (4%)	3,774	39.7	17%	4,134	41.1	21%	5,109	44.6	33%
Higher estimate of annual loss-to-follow-up (6%)	3,274	39.2	16%	3,530	40.5	19%	4,168	43.6	29%
Total number of deaths decreased/increased to UNAIDS estimate	3,351	39.3	16%	3,599	40.5	20%	4,208	43.6	29%

2.4.9 Exploratory modelling by risk group

Different ageing patterns are likely to occur in the different risk groups due to the epidemiological differences between these groups (e.g. in mean age of infection and mortality rates etc [188,196-198]).

In Ireland, individual level data on the risk factor and ages of diagnosed cases has only been available since a case-based voluntary reporting system was established by the HPSC in 2002 (with 2003 being the first full year of data collection). As can be seen in Figure 2-16 the mean age of notified cases differs across risk groups and has increased over time, except for the MSM risk group whose mean age at notification had decreased from 36.5 years in 2003 to 33.5 years in 2014.

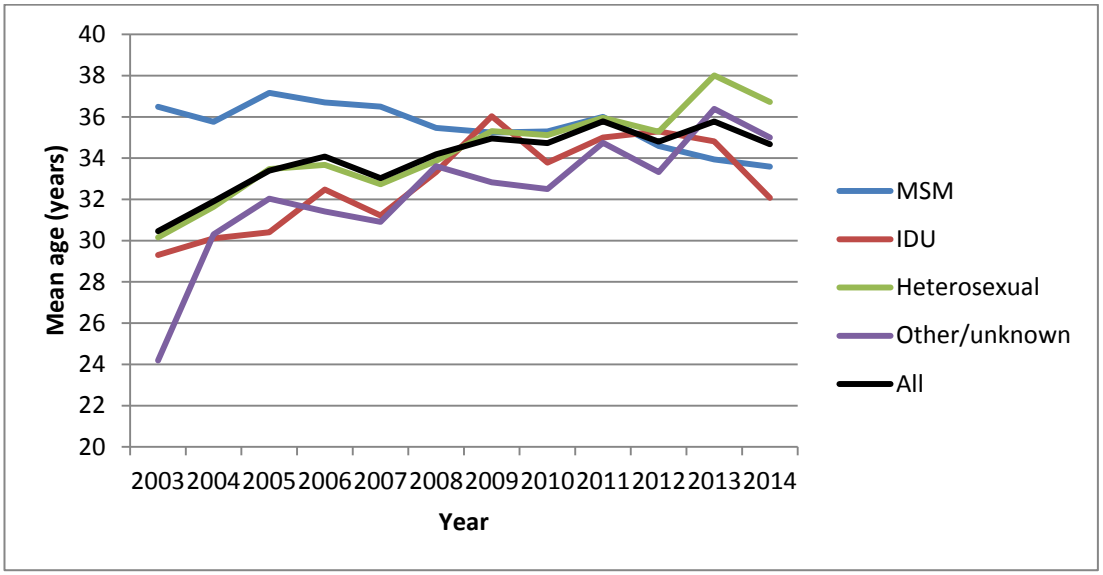


Figure 2-16. Average age of notified cases in Ireland 2003-2014 by risk group (Source of data: HPSC)

In order to examine possible differences in the ageing of the patients in care by risk group we ran the validated model separately for five different groups of cases:

1. Cases notified before 2003 (pre-2003)
2. MSM notified from 2003 onwards (MSM)
3. IDU notified from 2003 onwards (IDU)
4. Heterosexuals notified from 2003 onwards (Heterosexual)
5. Other/unknown notified from 2003 onwards (Other/unknown)

The validated model (model 2a) used number of HIV related deaths as estimated by the GBD study, however the estimated number of deaths from the GBD study is only broken down by age and not by risk factor. In order to use this model we had to assume that HIV-related deaths were distributed proportionally across risk groups. In reality this assumption is likely to underestimate deaths in risk groups with poorer HIV outcomes (such as IDUs and heterosexuals) and overestimate deaths groups with better outcomes (e.g. MSMs).

As empiric data on the age breakdown of patients in care by risk factor and year of notification was not available, it was also not possible to validate the results of this modelling, and all results should be interpreted with caution.

Breakdown of patients in care

The total number of patients in care by risk group is shown in Figure 2-17. By 2012 it was estimated that only 27% of patients in care had been diagnosed prior to 2003, by 2020 it is estimated that this proportion will have decreased to 14%.

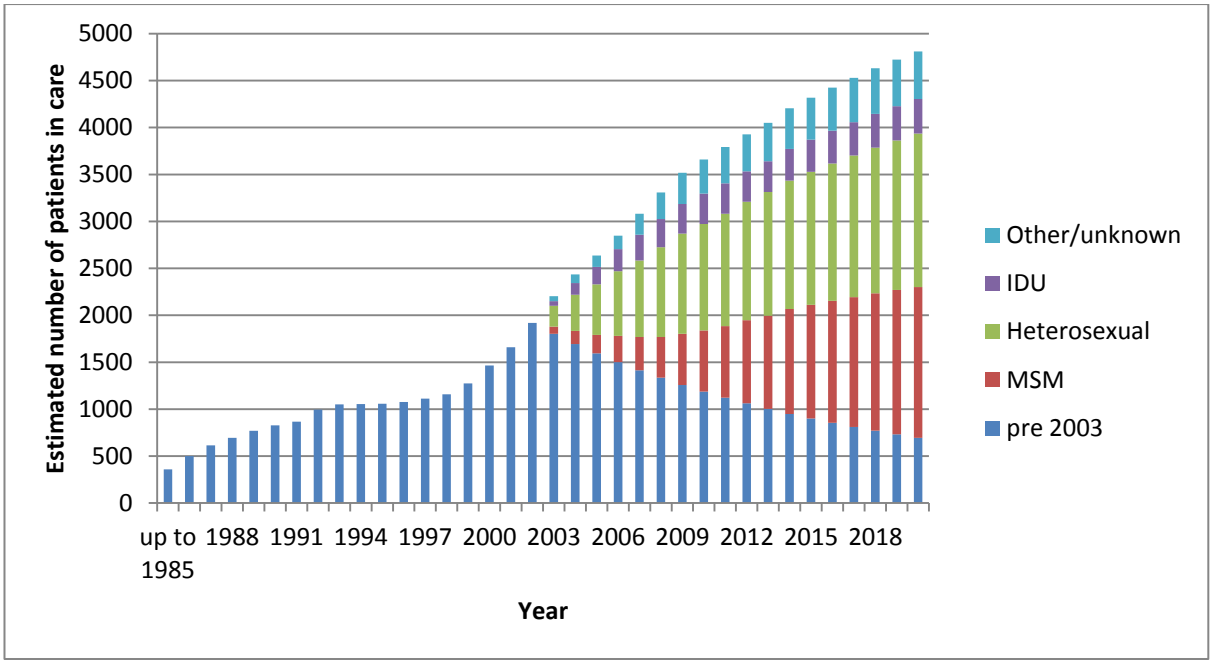


Figure 2-17. The estimated total number of HIV patients in care in Ireland by year and risk group (pre-2003 are cases notified prior to 2003 whose risk factor is not known).

MSMs

The estimated changes in the age distribution of MSMs in care notified since 2003 is shown in Figure 2-18. In 2003 approximately 9% of MSMs in care were ≥50 years of age, by 2012 this had increased to 17% and it is estimated to continue to increase to 22% by 2020. The mean age of MSM patients in care (also shown on Figure 2-18) has also increased by 4.5 years over the same time period (36.5 years in 2003 to 41 years in 2020).

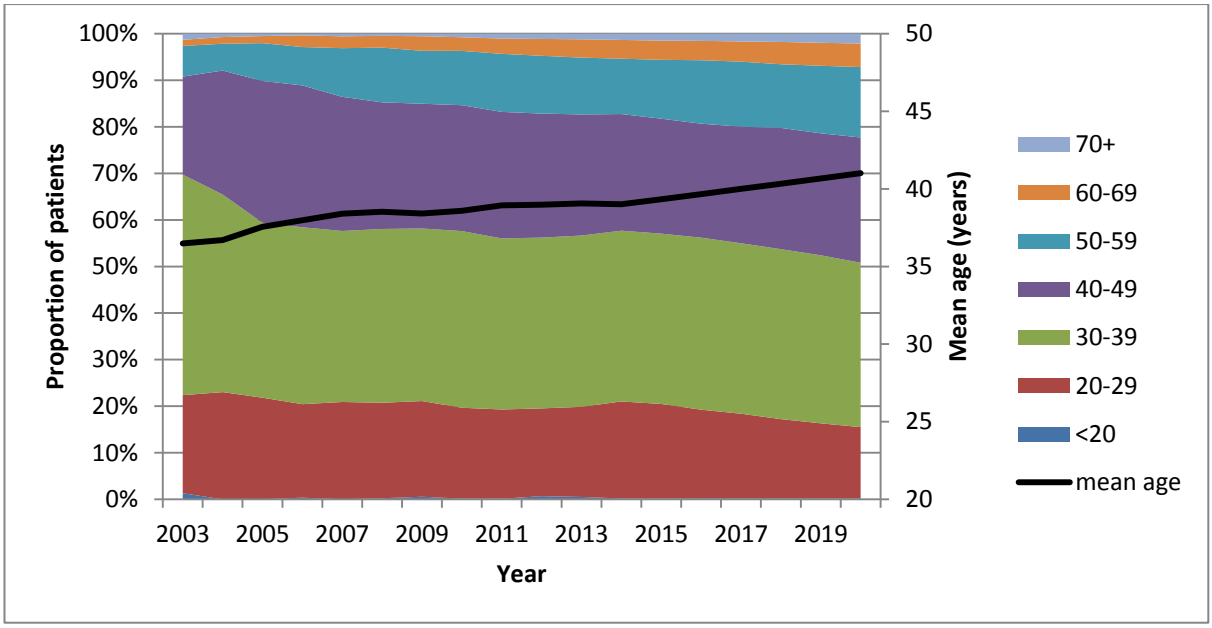


Figure 2-18. Estimated age profile and mean age of MSM HIV patients (notified since 2003) in care

Heterosexuals

The estimates of the changing age profile of the patients in the heterosexual risk group appear to be more dramatic than in the MSM patients (Figure 2-19) , with an increase in mean age of 13 years (from 30 years in 2003 to 43 years in 2020) with a 10-fold increase in the proportion of patients aged ≥50 years, from 2% in 2003 to over 24% in 2020.

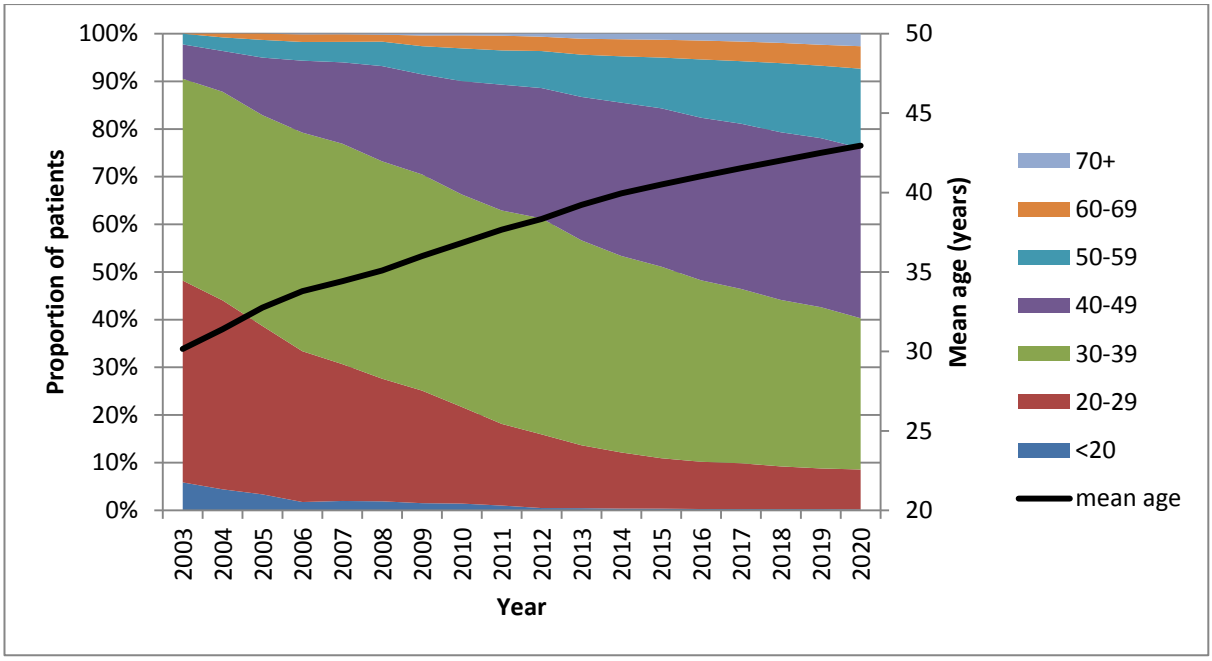


Figure 2-19. Estimated age profile and mean age of heterosexual HIV patients (notified since 2003) in care

IDUs

The scale of the ageing of the IDU patients is similar to the heterosexual population in that we have estimated a 14 year increase in mean age between 2003 and 2010 (from 29 years to 43 years) and 23% of patients projected to be aged ≥50 years by 2020 (Figure 2-20).

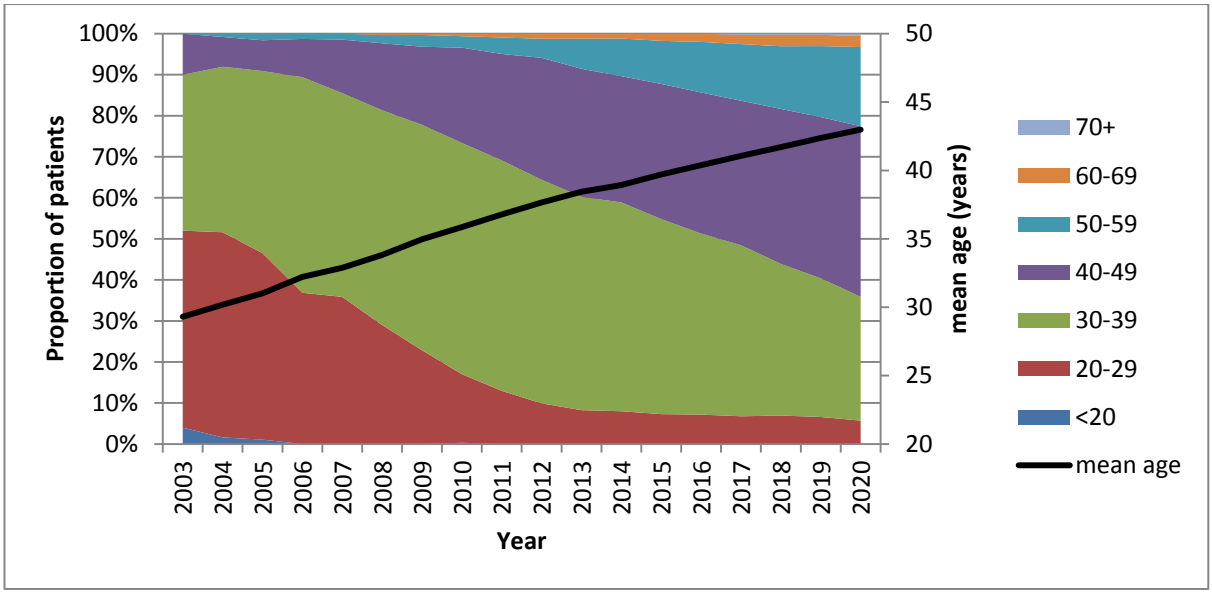


Figure 2-20. Estimated age profile and mean age of IDU HIV patients (notified since 2003) in care.

Comparison of risk groups

The estimated changes in the mean age of patients in care by risk group are shown in Figure 2-21. The mean age of MSMs has increased the least (0.3 years annual on average between 2003 and 2020), with the mean age of all other groups increasing by 0.8-1.1 years annually over the same time period.

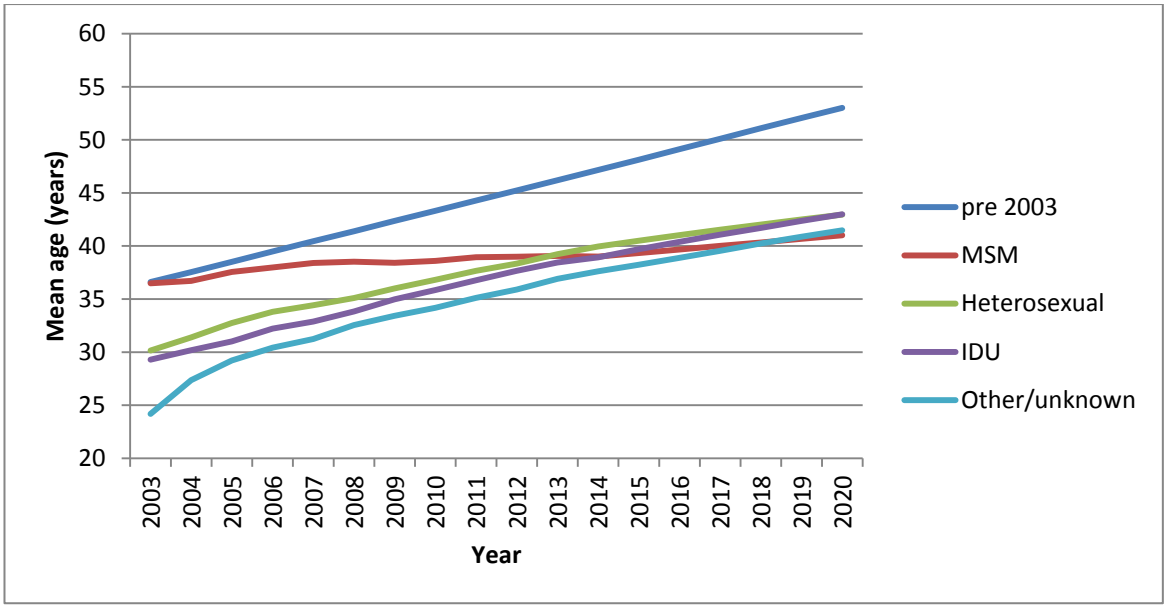


Figure 2-21. Estimated mean age of patients in care in Ireland by risk group

As would be expected the proportion of patients aged ≥50 years is increasing most rapidly in the group of patients diagnosed prior to 2003, with an estimated 65% of this group being aged ≥50 years by 2020 (Figure 2-22). The results of this modelling also illustrate that patients in the ≥50 year age group are still relatively young. In 2012 50% of patients estimated to be aged ≥50 years were aged between 50 and 54 years and only 10% of patients aged ≥50 years were aged ≥65 years (2% of all patients) (Figure 2-23).

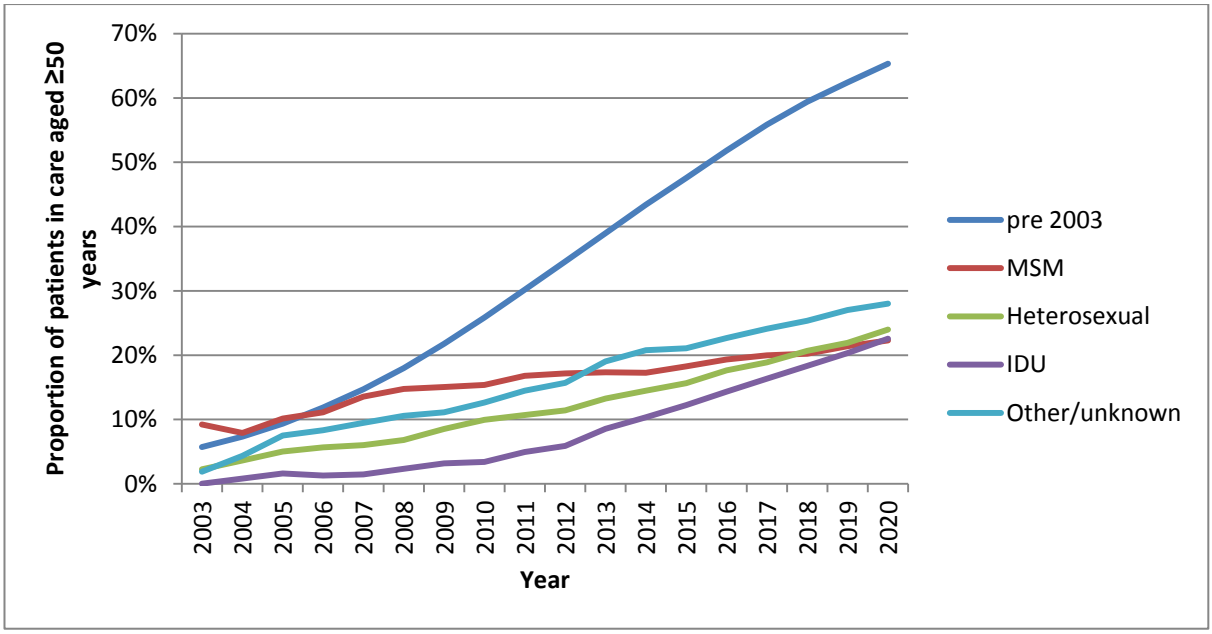


Figure 2-22. The proportion of patients in care in Ireland aged ≥50 years each year by risk group

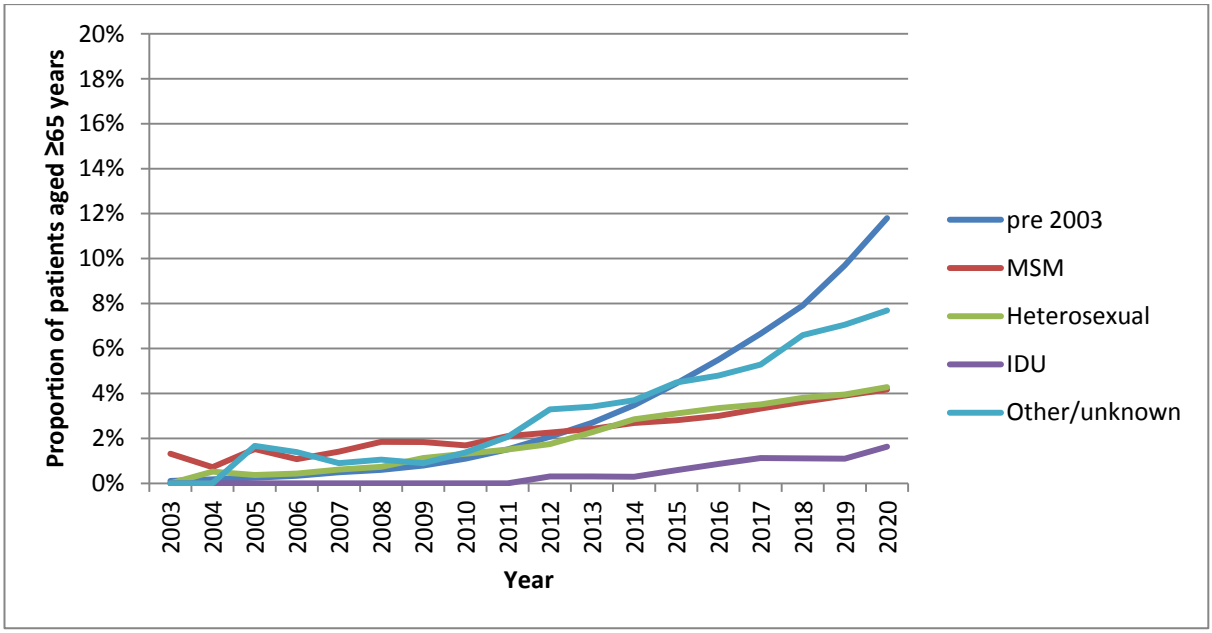


Figure 2-23. The proportion of patients in Ireland aged ≥ 65 years in care each year by risk group

Although the age profile of the MSM population in care is estimated to be changing more slowly than other risk groups, in terms of absolute patient numbers MSMs are still projected to account for one quarter of patients aged ≥50 years in 2020 (Figure 2-24).

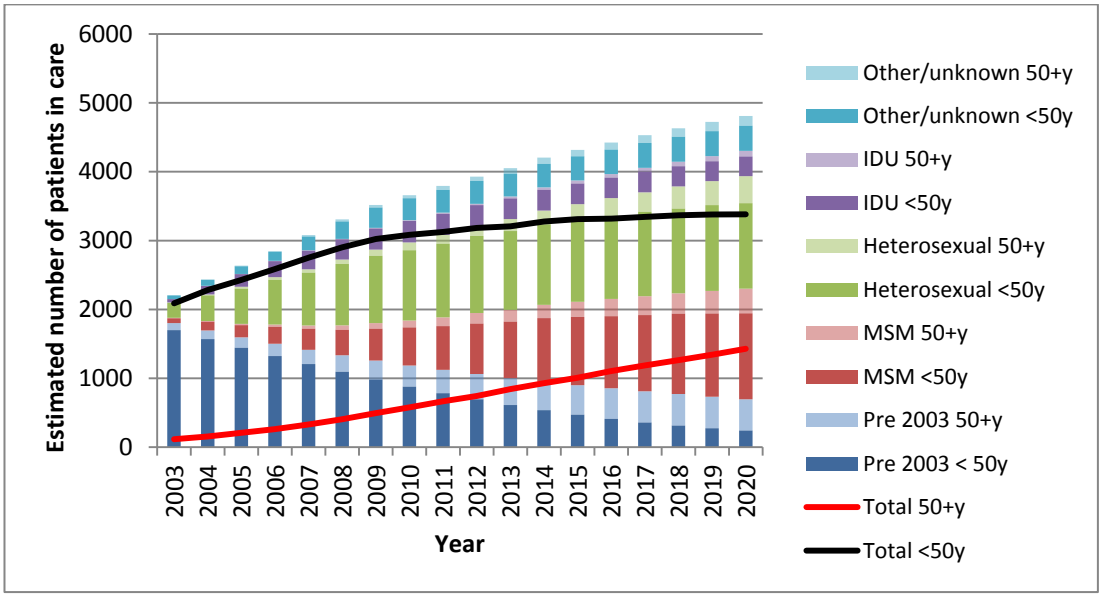


Figure 2-24. The estimated number of patients in care aged ≥50 years by year and risk group

2.5 Discussion

Accurate data on the epidemiology of any disease, including data on its prevalence and demographic characteristics is essential for health service planning. While there has been comprehensive case-based reporting of new HIV diagnoses in Ireland since 2003, there is very little data on the prevalence of HIV, the demographic characteristics of the national HIV cohort and until recently, on the total number of patients accessing services nationally. In the absence of empiric data mathematical models can provide useful data on the epidemiology of infectious diseases and the

potential impact of control programmes. Some modelling of the HIV epidemic in Ireland was carried out in the pre-HAART era based on HIV transmission in the injecting drug using population [176,199]. Since then there has been no published attempt to model the HIV epidemic in Ireland, due to the lack of many of the key pieces of information needed for the accurate modelling of HIV epidemics, such as age at infection, mortality data, stage at diagnosis (CD4 or CDC classification) and proportion of patients in treatment.

Despite the lack of available data, we felt it was necessary to attempt to estimate the number of patients as accurately as possible to inform the estimated national cost of providing outpatient care in 2012. We have also attempted to generate estimates of the age distribution of patients due to the resource implications the ageing of the HIV population is likely to have, and have used the model developed to make short term predictions, up to the year 2020, of the total number and age breakdown of patients in HIV care in Ireland. We estimated that the total number of people in care in 2012 was approximately 3,820 (ranging on sensitivity analysis from 3,668 to 4,134), and if the number of cases diagnosed annually remains stable, project that by 2020 4,607 patients will be attending care for HIV in Ireland. The mean age of cases was estimated to be 40.8 years, and the mean age had increased annually by an average of 0.49 years each year in recent years (2005-2014), with the proportion of patients aged ≥50 years increasing by 1.5% each year over the same period. When compared to other developed countries, the age profile of HIV patients in care in Ireland appears slightly younger [141,144,167,200], although it is difficult to make direct comparisons because of differences in the definitions and

methods used to generate these estimates. In reality, in some cases the difference may be even greater, as estimates of the proportion of people living with diagnosed HIV who are in the older age groups are likely to be lower than the proportion of people in care in the same age groups as engagement in care increases with age [201]. For example, in the US it was estimated that 35% of people living with diagnosed HIV in 2012 were ≥50 years [202] but data from a survey of patients in care for the same year (the Medical Monitoring Project) estimated that 40% of adult patients (>18 years) in care were ≥50 years [203]. Despite the differences in the proportion of older patients across countries, however, the rate at which HIV populations are ageing appears consistent across jurisdictions (Figure 2-14).

Although the results of the exploratory modelling of the ageing of patients in care stratified by risk group are unvalidated and should be interpreted with caution, it is interesting to see the possible differences in age trends – with the MSM population ageing at a slower rate than the other risk groups. This is somewhat different to what has been described in the literature in the US where the rate of ageing of MSMs in care appears similar to other risk groups [134], and is a reflection of the ongoing transmission of HIV in young MSMs in Ireland [82].

2.5.1 Strengths and limitations

Due to the lack of data available, only very rudimentary calculations were used to model the numbers of patients in care each year, and it was unclear which estimates of age and deaths were the most appropriate to use. In light of this, several variations of the model were performed and the results of all the models were validated against observed data from a prevalence study of patients in care in

2009/2010 [85]. Only one model was found not to result in estimates significantly different from the observed data. This model was selected as the final model and uncertainty in the final model was investigated using one-way sensitivity analysis, varying the mean age (pre 2002), loss-to-follow-up and number of deaths. The level of variation of the input variables in the sensitivity analysis was informed by the data available.

There are also major limitations to the estimates generated. A lack of data on age at diagnosis made it necessary to construct age distributions for years pre 2003 based on mean ages of diagnoses. For years before 1992 the mean age was based on a single study of attenders at one Dublin clinic [176], while between 1992 and 2002 age information from first positive samples sent to the NVRL was used, which was likely to overestimate the mean age at diagnosis. Reliable routine data on deaths in HIV patients is also limited in Ireland and we had to use the estimated number of deaths from a modelling study, which had its own assumptions and limitations [190].

We relied on a published estimate of 5% loss-to-follow-up each year in the UK, however, this rate may not be appropriate for use in Ireland, as several factors may have resulted in higher out-migration of HIV patients in Ireland compared to the UK or other developed countries. At the beginning of the HIV/AIDS epidemic in the 1980s and early 1990s Ireland had a comparatively low proportion of MSM cases. This may have been due to underreporting of MSM as a risk factor as a result of the particular cultural and religious factors present in Ireland at that time (e.g. illegality of homosexual activity) [204], however these same factors also resulted in high

emigration rates (either permanent or temporary) of MSMs [205], and HIV positive MSMs in particular may have travelled abroad for HIV diagnosis and/or treatment particularly in the early years of the epidemic, when stigma was high and expertise in Ireland was limited (the first infectious disease consultant was appointed in Ireland in 1993, previously there had been a single consultant in genitourinary medicine appointed in 1987 providing care for HIV patients). In addition, starting in the late 1990s there was a large rise in notified HIV in heterosexuals the majority of whom originated from sub-Saharan Africa [206]. A substantial proportion of these cases were likely to have been asylum seekers as there was a sharp increase in the number of people seeking asylum in Ireland around that time [207] and the prevalence of HIV in asylum seekers is 1.7% [96]. It is unclear what proportion of HIV positive asylum seekers remain in the county, given that the success rate for asylum applications generally is low (around 10% [207]). A further complication is the possibility of patients choosing to attend a consultant privately for their routine HIV care, and so be "lost" to the public system. The number of patients attending private HIV care nationally is unknown. Temporary loss-to-follow-up was also not included in the model.

The model used was a very simple deterministic model, using population averages and did not take into account changes in individual patients' status over time. The main model was not stratified for any clinical (e.g. CD4 counts, AIDS diagnosis, treatment status) or demographic (e.g. gender, risk group) factors, apart from age at diagnosis. We did attempt to explore possible differences be risk group for cases notified since 2003, however it was not possible to validate the results of the

stratified modelling, and the assumption was made that HIV-related deaths were distributed evenly across risk groups, which is unlikely to be the case in reality.

There was also only one year of empiric data to validate the results of the main model against, it is possible that the final model selected produced an age-distribution similar to the observed data by chance, and if further years of observed data had been available the model would have been proved to produce invalid results.

In conclusion, we estimate that in 2012 there were approximately 3,820 HIV patients in care in Ireland, and that approximately 20% of the patients in care were ≥ 50 years of age. Unless the new number of diagnoses decreased we estimate that by 2020 the total number of patients in care will have increased by approximately 20% and nearly one third of patients in care will be ≥50 years of age. This is the first attempt to quantify the size and age breakdown of the HIV patients in care in Ireland in the HAART era, and as such will feed into our estimation of the current cost of outpatient care at a national level. In the absence of the data required to allow more sophisticated modelling of the HIV epidemic here these results provide a basis for assessing the potential rate of ageing of the HIV population in Ireland.

3 Determinants of HIV outpatient utilisation: A systematic review

Aline Brennan

Deirdre Morley

Aisling O'Leary

Colm J Bergin

Mary Horgan

This paper was published in AIDS and Behavior in 2015 (see Appendix 1)

3.1 Abstract

Demands on HIV services are increasing as a consequence of the increased life-expectancy of HIV patients in the HAART era. Understanding the factors that influence utilization of ambulatory HIV services is useful for planning service provision. This study reviewed factors associated with utilization of hospital based HIV out-patient services. Studies reporting person-based utilization rates of HIV-specific outpatient services broken down by patient or healthcare characteristics were eligible for inclusion. The Andersen Behavioural Model was used to organise the information extracted into pre-disposing, enabling and need components. Ten studies were included in the final review. Older age, private insurance, urban residence, lower CD4 counts, a diagnosis of AIDS, or anti-retroviral therapy (ART) were associated with higher utilization rates. The results of this review are consistent with existing knowledge regarding HIV patients' use of health services. Little information was identified on the influence of health service characteristics on utilization of out-patient services.

3.2 Introduction

The emergence of HAART for the treatment of HIV infection in the mid-1990s has had profound consequences for both those living with HIV and the healthcare systems providing care for them. A person diagnosed with HIV today can have a near normal life expectancy [208]. A recent modelling study estimated that the median life expectancy of people living with HIV after entry to healthcare is over 40 years [9]. Continuing transmission of HIV, combined with the reductions in mortality and increased life-expectancy resulting from HAART, means that both the overall size and the age profile of the HIV population are increasing. These changes will inevitably increase the demands placed on HIV services worldwide.

Utilization of healthcare services is influenced by many factors which operate at individual, healthcare provider and societal levels. Examination of healthcare utilization patterns can be used to identify sub-groups of patients who are either under- or over-utilizing services. Under-utilization of services has consequences for the patient, as it has been shown that patients not fully engaged in care have poorer outcomes [76], while over-utilization is an inefficient use of health system resources. International guidelines for the care, management and treatment of HIV patients recommend that patients are monitored 2-4 times per year, depending on the individual needs of the patients [3,41,75]. However there is still debate on the optimal frequency of monitoring [77,78]. While quality indicators, such as the recent HIV/AIDS Bureau performance measures [209] have been developed which include measures of visit frequency, these measure the proportion of patients meeting a minimum standard and do not provide information on the volume of

care being provided. It is necessary to have information on the volume of resources used by patients, and the most important factors which influence patients' utilization of services, to accurately estimate the consequences of the changing population characteristics on future service demand and cost.

The Behavioural Model was originally developed by Andersen in the 1960s to explain why people use healthcare services [210]. The model initially categorised explanatory factors into three components: predisposing, enabling and need factors. Later versions of the model also incorporated health behaviour and outcomes, with feedback loops to reflect the dynamic relationships between outcomes, use of services and explanatory factors [211]. It has been widely used since both as a theoretical framework for explaining why people use health services [212], and as an organizational framework for reviewing determinants of health service utilization in a variety of settings and diseases [213-215].

A previous comprehensive review of HIV healthcare utilization performed by Uphold and Mkanta (2005) described some variation in use of out-patient services [216]. However, their review did not focus specifically on outpatient services, was not systematic and many of the articles reporting out-patient utilization pre-dated or were from the early HAART era. Other reviews have focused on specific aspects of HIV care such as retention and engagement [217], cost [130] or use of specific services such as prevention services [218]. To our knowledge no review of the determinants of HIV out-patient utilization has been carried out to date.

The aim of this review was to identify any patient and/or healthcare related factors reported in the literature to be associated with HIV outpatient utilization in the HAART era.

3.3 Methods

The methodology for carrying out this review was based on published guidance for conducting and reporting systematic reviews [219-221].

The electronic databases PubMed, EMBASE, EconLit and CINAHL (EconLit and CINAHL via EBSCO) were searched for articles published between 01/01/1997 and 01/03/2013. Keyword searches combined common terms for HIV (Human immunodeficiency virus OR HIV OR AIDS), healthcare (ambulatory care OR hospital OR out-patient OR outpatient), utilization (utilization OR utilisation OR cost OR expenditure), and patient characteristics (patient characteristics OR determinants OR predictors). An example of the full search strategy can be seen in Appendix 2. In addition, the reference lists of articles which underwent full review were manually searched.

Any article which reported person-based utilization rates, or rate-ratios, of adult hospital-based HIV outpatient services, broken down by patient or healthcare factors were eligible to be included, regardless of study design. Due to the impact of HAART on patterns of healthcare utilization, only articles published since 1997 or reporting data for a time period when HAART was routinely available were reviewed.

Studies were excluded if they reported utilization of out-patient care which was not hospital-based (e.g. community, general practitioner, dental, complementary, prevention or home care services); or was not HIV specific (e.g. included outpatient visits to non-HIV services). Studies solely reporting utilization data of sub-groups of patients with specific co-morbidities (e.g. tuberculosis patients, haemophiliacs) and data on patients participating in clinical trials were excluded unless relevant information was reported on patients receiving usual care. Modelling studies were excluded unless they reported original utilization data. Studies which did not contain original utilization data (reviews/opinion pieces), were not peer-reviewed, or were published only in abstract form or in a language other than English, were also excluded.

Data forms for extraction of study characteristics and quality assessment were developed based on published guidelines [219]. Data was extracted from included articles by a single reviewer (AB) and independently checked for completeness and accuracy by a second reviewer (DM).

Information was extracted on general characteristics as well as analysis and reporting of the study results. The risk of bias (selection, information, other bias), choice of outcome measure, statistical analysis, quality of reporting, generalizability of results, and statements of funding/conflicts of interest were extracted and used to assess the overall quality of each study.

The behavioural model for vulnerable populations was used as a framework for categorizing the results of this review into predisposing, enabling and need factors using traditional and vulnerable domains [222].

3.4 Results

3.4.1 Study characteristics

A total of 10 articles were included in the final review. The number of articles excluded at each stage and reasons for exclusion are shown in Figure 3-1.

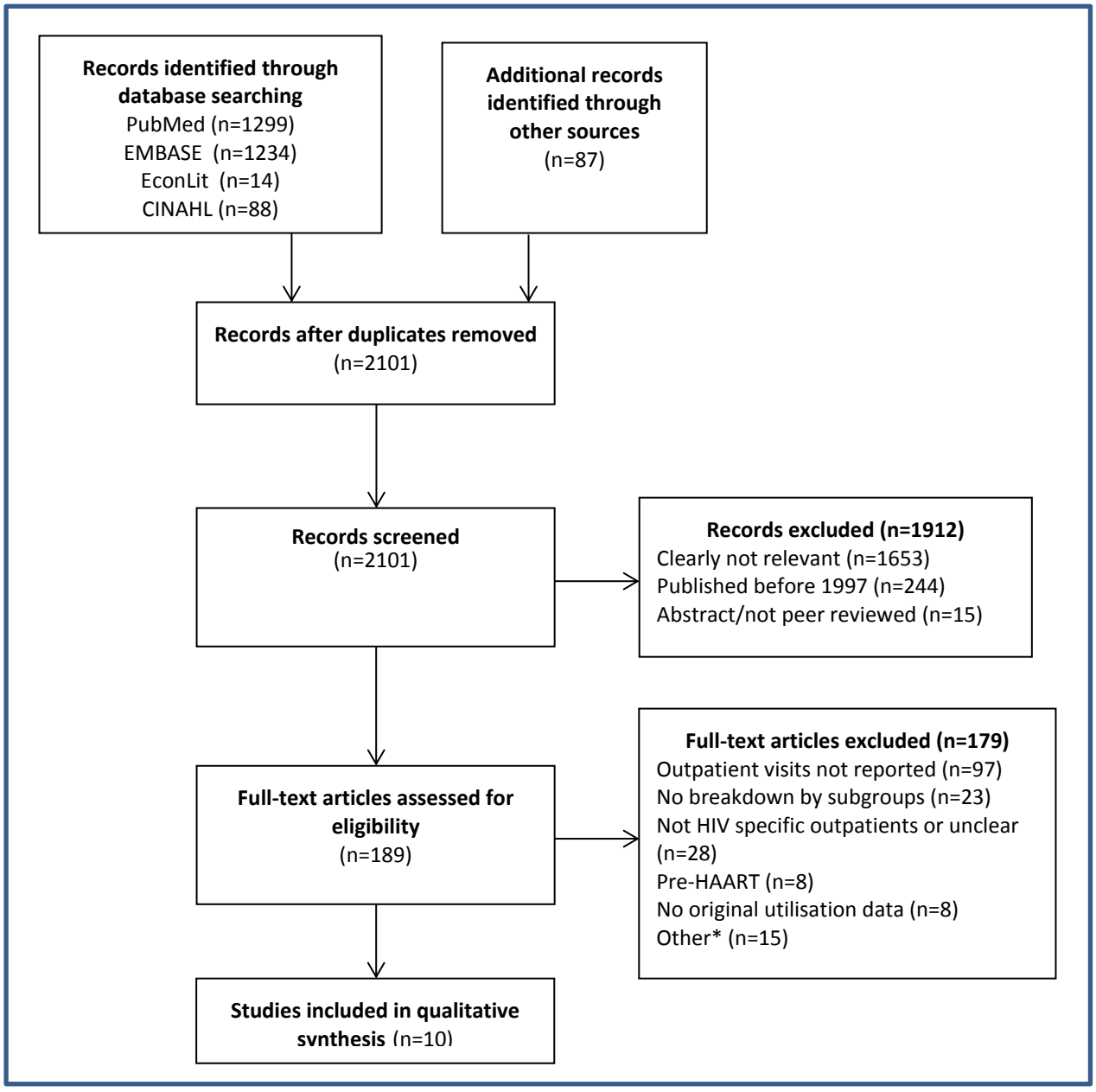


Figure 3-1. Flow chart of study selection

*Other: Mother-to-child-transmission prevention (n=4), data only relating to a specific subgroup of patients (n=3), not hospital based (n=2), same/overlapping data as another article (n=3), non-English (n=1), clinical trial, no usual care arm (n=2)

A summary of the study characteristics can be seen in Table 3-1. Four of the studies included were carried out in the United States (US) [223-226]. Of these, two reported on data collected as part of the HIV Research Network (HIVRN) [223,225], however as these studies reported data from different years both were retained in this review. The remaining studies were spread across Europe [138,227,228], Africa [229,230], and Asia [231].

The quality of seven of the articles reviewed was assessed as average or good, while three were assessed to be of poor quality (Table 3-2). The main issues affecting methodological quality were a lack of information on the sources of data used, and a low level of statistical analysis. Only two papers reported multivariate analysis [223,226].

A summary of the results of the studies can be seen in Table 3-3 and Table 3-4.

3.4.2 HIV outpatient use

3.4.2.1 Predisposing characteristics

Three of the 10 articles included in the review reported utilization rates by the traditional predisposing demographic characteristics of gender, age and ethnicity [223,226,228]. Additional predisposing characteristics specific to vulnerable populations reported in the included studies were residency/immigration status [138,228], and route of infection [223,226,228].

Table 3-1. Characteristics of included studies

Reference	Country	Patient characteristics	Type of study	Data collection	Source of data	Time period of data	Number of patients included	Duration of follow-up:
Bikilla et al., 2009 [229]	Ethiopia	No ART OR ART, >= 15 years old	Comparison of 2 cohorts overlapping in time	Retrospective	Existing clinic database	Non-ART: Jan 2003-Apr 2004 ART: Aug 2003-Mar 2006	Before: 203 After: 209	before : up to 15.2 months after: up to 31.2 months
Cook et al., 2009 [228]	UK	All attendees	Cohort	Retrospective (every 6 months)	Enhanced HIV surveillance system	Jan 2005-Jun 2006	3,983	up to 18 months
Fleishman et al., 2005 [223]	US	>=18 years old, in longitudinal HIV primary care	Repeat cross-sectional	Retrospective	Existing admin/hospital database & medical records	2000 2001 2002	13,392 15,211 14,403	1 year
Garattini et al., 2001 [227]	Italy	AIDS or Non-AIDS by CD4	Cohort	Prospective	Physician collected	Aug 1997-Jul 1998	483	1 year
Howe et al., 2010 [226]	US	>= 18 years attending care, attended at least 1 appointment subsequent to baseline with laboratory measurements available	Cohort	Prospective	Existing admin/hospital databases & medical records, patient interview	2001-2007	1,636	up to 7 years max
Larson et al., 2013 [230]	Kenya	1st year of ART, >=18 years old, not pregnant, files available	Cohort	Retrospective	Medical records	2007-2008	360	12 months
Paton et al., 2006 [231]	Singapore	all attendees with at least 3 months of follow-up, who either never had ART, or had only dual or only HAART. Singaporeans or permanent residents.	Cohort	Not specified	Existing clinical database	1996-2001	764	up to 5 years max

Reference	Country	Patient characteristics	Type of study	Data collection	Source of data	Time period of data	Number of patients included	Duration of follow-up:
Siddiqui et al., 2009 [224]	US	Commercial health plan members, 2 medical claims with HIV diagnosis, or 1 medical claim and 1 prescription for ARV, 12 months continuous enrolment	Cohort	Retrospective	Claims database	Jan 2005-Jul 2007	12,189	1 year
Velasco et al., 2012 [138]	Spain	All attendees	Cohort	Retrospective	Existing admin/hospital database	2003-2005	372	up to 3 years
Wilson et al., 2011 [225]	US	>=18 years, in longitudinal primary care	Cross-sectional	Retrospective	Existing admin/hospital database & medical records	2005	8,824	1 year

Table 3-2. Quality assessment of included studies

Reference	Assessment of selection bias	Assessment of Information bias	SE, SD or 95%CI of means reported	Multivariate analysis	Other quality issues	Overall assessment of quality
Bikilla et al., 2009 [229]	Unlikely	Unlikely	Yes	No	The cohort of patients not on ART was earlier (but overlapping) in time than the cohort on ART. The ART cohort contained a much greater proportion of AIDS patients.	Average
Cook et al., 2009 [228]	Unclear	Unlikely	Yes	No	Time period used for calculation of rates not clearly reported	Average
Fleishman et al., 2005 [223]	Unclear	Unlikely	Yes	Yes		Good
Garattini et al., 2001 [227]	Unlikely	Unlikely	Yes	No		Good
Howe et al., 2010 [226]	Unlikely	Unlikely	Yes	Yes		Good
Larson et al., 2013 [230]	Likely	Unlikely	No	No	Rates specific to individual sites, would not be generalizable	Poor
Paton et al., 2006 [231]	Unlikely	Unlikely	No	No	No details given about recruitment of participants	Poor
Siddiqui et al., 2009 [224]	Unlikely	Unlikely	Yes	No	Overall generalizability may be an issue as all participants were employees	Average
Velasco et al., 2012 [138]	Likely	Unlikely	Yes	No	Time period of utilization data unclear	Poor
Wilson et al., 2011 [225]	Unclear	Unlikely	Yes	No		Average

SE, standard error SD standard deviation CI, confidence interval

Table 3-3. Summary of results of included studies

Reference	Predisposing	Enabling	Need
Bikilla et al., 2009 [229]			**ART**: patients on ART (AIDS and non-AIDS) had significantly more outpatient visits per year than non-ART patients **AIDS** patients: no significant differences between the number of visits of AIDS patients compared to non-AIDS patients within the groups of patients either on ART or not on ART
Cook et al., 2009 [228]	**Gender**: no significant difference in number of visits. **Age group**: younger and older age groups had significantly more visits than 25-34 year olds. **Ethnicity**: black Africans had significantly fewer visits than whites. **Route of infection**: mother to child and MSM had significantly more visits than heterosexuals. **Residency**: Asylum seekers and overseas students had significantly fewer visits than UK and other non-UK residents.	**Deprivation & urban category**: No significant differences.	**Level of ART**: those on quadruple therapy had significantly more visits than those on mono/dual/triple therapy, who had significantly more visits than those not on ART.
Fleishman et al., 2005 [223]	**Gender**: females had significantly more visits than males. **Age group**: number of visits increased significantly with age group. **Ethnicity**: Hispanic patients had significantly more visits then whites. **Route of transmission**: Heterosexuals and IDUs had significantly fewer visits than MSMs.	**Insurance**: compared to those with private insurance those with medicaid and medicare had significantly more visits and those uninsured had significantly fewer visits.	**CD4**: number of visits increased significantly as CD4 decreased. **VL**: those with VL < 10,000 had a significant, but slight, decrease number of visits compared to those with VL > 100,000. **HAART**: those on HAART had significantly more visits than those not receiving HAART.

Reference	Predisposing	Enabling	Need
Garattini et al., 2001 [227]			**ADI and CD4 category**: No significant differences.
Howe et al., 2010 [226]	**Gender**: no significant difference. **Age group**: visits increased significantly with age. **Ethnicity**: no significant difference. **Risk factors**: no significant differences.	**Insurance**: no significant differences. **Urban area**: no significant difference. **Distance to clinic**: no significant difference. **Care first initiated in the study center**: no significant difference.	**CD4**: those with CD4 > 350 had significantly fewer visits than those with CD4 < 200. **VL**: no significant difference. **AIDS**: those with a clinical diagnosis of AIDS had significantly more visits than those not diagnosed with AIDS. **ART**: those on cART had significantly more visits than those not on cART
Larson et al., 2013 [230]		**Site**: utilization varied by site, unable to assess if differences were significant.	
Paton et al., 2006 [231]			**CDC stage A**: visits increased from no ART to dual ART to HAART groups (unable to assess significance of differences). **CDC stage B**: More frequent visits in all categories compared to stage A patients (unable to assess significance of differences). Those receiving dual ART had highest utilization, followed by patients on HAART and then patients not on ART (unable to assess significance of differences). **CDC stage C**: similar patter to stage B patients, but rates higher in each category (unable to assess significance of differences).
Siddiqui et al., 2009 [224]			**HIV associated weight loss**: those with weight loss had significantly more visits than those without weight loss.
Velasco et al., 2012 [138]	**Immigrant**: no significant difference.		

Reference	Predisposing	Enabling	Need
Wilson et al., 2011 [225]		**Area of residence**: utilization increased significantly from rural to peri-urban to urban area of residence for all patients.	**HAART patients only**: more frequent visits on average than all patients combined, same pattern of utilization for area of residence (unable to assess significance of differences).

S, significant. NS, not significant. U, unable to assess significance. IDU, injection drug use. VL, viral load. ADI, AIDS defining illness. OI, opportunistic infection. (c)ART, (combined) anti-retroviral therapy.

Table 3-4. HIV outpatient visit rates and relative rates by patient subgroup reported by included studies

Group	Reference	Year(s)	Denominator	Category	Rate (95% CI)	RR (95% CI)	RR_{adj} (95% CI)
Predisposing characteristics							
Gender	Cook et al., 2009 [228]	2005-2006	Annualised rate (based on 6 month periods)	Male	6.1 (5.9-6.2)		
				Female	5.8 (5.6-6.1)		
	Fleishman et al., 2005 [223]	2000-2002	Calendar year	Male	5.46-5.90		ref
				Female	5.86-6.44		1.12 (1.09-1.14)
	Howe et al., 2010 [226]	2001-2007	Person-months	Female		0.96 (0.92-1.00)	1.01 (0.96-1.07)*
Age	Cook et al., 2009 [228]	2005-2006	Annualised rate (based on 6 month periods)	0-14	6.8 (5.9-8.0)		
				15-19	7.4 (5.6-9.8)		
				20-24	5.5 (4.9-6.2)		
				25-29	5.6 (5.2-6.0)		
				30-34	5.4 (5.1-5.7)		
				35-39	5.7 (5.5-6.1)		
				40-44	6.5 (6.1-6.8)		
				45-49	6.9 (6.5-7.3)		
				50-54	6.4 (5.8-6.9)		
				55-59	6.2 (5.5-7.0)		
				60+	6.7 (6.0-7.4)		
	Fleishman et al., 2005 [223]	2000-2002	Calendar year	18-30	4.12-4.87		ref
				31-49	5.55-6.04		1.13 (1.10-1.16)
				50+	6.39-6.86		1.27 (1.22-1.31)
	Howe et al, 2010 [226]	2001-2007	Person-months	per 10 years		1.07 (1.05-1.09)	1.06 (1.04-1.09)*

Group	Reference	Year(s)	Denominator	Category	Rate (95% CI)	RR (95% CI)	RR_{adj} (95% CI)
Ethnicity	Cook et al., 2009 [228]	2005-2006	Annualised rate (based on 6 month periods)	White	6.1 (6.0-6.3)		
				Black Caribbean	6.5 (5.2-8.2)		
				Black African	5.8 (5.5-6.0)		
				Black Other	6.5 (4.7-9.0)		
				Indian/Pakistani/Bangladeshi	5.5 (4.6-6.6)		
				Other Asian/Oriental	5.5 (4.2-7.1)		
				Other/Mixed	6.0 (5.1-7.1)		
				Unknown	3.6 (2.5-5.1)		
	Fleishman et al., 2005 [223]	2000-2002	Calendar year	White	5.28-6.02		ref
				Black	5.10-5.68		1.02 (0.99-1.04)
				Hispanic	6.74-7.02		1.11 (1.08-1.14)
				Other	5.93-6.17		1.04 (0.97-1.12)
				Missing ethnicity	3.59-6.27		0.93 (0.87-1.00)
	Howe et al., 2010 [226]	2001-2007	Person-months	African American		0.95 (0.91-0.99)	0.96 (0.92-1.00)*
Residency/immigration status	Cook et al., 2009 [228]	2005-2006	Annualised rate (based on 6 month periods)	UK	6.1 (6.0-6.3)		
				Asylum seeker	5.5 (5.1-6.0)		
				Overseas student	5.2 (4.5-6.0)		
				Other non UK	6.4 (5.8-6.9)		
				Unknown	5.3 (4.8-5.9)		
	Velasco et al., 2012 [138]	2003-2005	study duration	Spaniard	5.8 (SD 4.7)		
				Immigrant	5.6 (SD 4.5)		

Group	Reference	Year(s)	Denominator	Category	Rate (95% CI)	RR (95% CI)	RR_{adj} (95% CI)
Route of transmission	Cook et al., 2009 [228]	2005-2006	Annualised rate (based on 6 month periods)	MSM	6.3 (6.3-6.5)		
				IDU	5.3 (4.5-6.2)		
				Heterosexual	5.7 (5.5-6.0)		
				Blood/tissue	5.9 (5.0-7.0)		
				Mother to child	7.2 (6.2-8.3)		
				Other/unknown	4.9 (3.9-6.1)		
	Fleishman et al., 2005 [223]	2000-2002	Calendar year	MSM	5.34-5.89		ref
				IDU	6.07-6.38		0.96 (0.93-0.99)
				Heterosexual	5.60-6.12		0.95 (0.93-9.8)
				MSM-IDU	6.62-6.79		1.06 (1.00-1.12)
				Heterosexual-IDU	5.77-6.10		1.04 (0.99-1.09)
				Other	4.35-5.42		0.87 (0.83-0.92)
				Missing	5.35-6.65		0.84 (0.81-0.88)
	Howe et al., 2010 [226]	2001-2007	Person-months	Intravenous drug use		1.05 (0.99-1.12)	1.03 (0.96-1.11)
				MSM		1.04 (1.00-1.08)	1.05 (1.00-1.11)*
Enabling characteristics							
Insurance	Fleishman et al., 2005 [223]	2000-2002	Calendar years	Private	4.53-4.95		ref
				Medicaid	6.36-6.76		1.12 (1.09-1.15)
				Medicare	6.25-7.38		1.22 (1.19-1.26)
				Ryan white/uninsured	4.28-5.32		0.97 (0.94-0.99)
				Missing insurance	2.04-4.42		0.59 (0.55-0.62)
	Howe et al., 2010 [226]	2001-2007	Person-months	None/other		ref	ref
				Private		1.07 (1.02-1.12)	1.04 (0.99-1.09)*
				Public		1.06 (1.00-1.11)	1.05 (1.00-1.11)*

Group	Reference	Year(s)	Denominator	Category	Rate (95% CI)	RR (95% CI)	RR_{adj} (95% CI)
Area of residence	Cook et al., 2009 [228]	2005-2006	Annualised rate (based on 6 month periods)	Not urban, least deprived	5.4 (4.8-6.0)		
				Urban, least deprived	6.1 (5.9-6.4)		
				Urban, average deprivation	6.1 (5.8-6.3)		
				Urban, most deprived	5.9 (5.7-6.2)		
	Wilson et al., 2011 [225]	2005	Calendar year	Rural	3.95		
				Peri-urban	4.4		
				Urban	5.24		
				Rural (patients on HAART)	4.02		
				Peri-urban (patients on HAART)	4.48		
				Urban (patients on HAART)	5.83		
	Howe et al., 2010 [226]	2001-2007	Person-months	Urban area		1.03 (0.98-1.08)	1.02 (0.97-1.07)*
				Distance to clinic per 50 miles		0.97 (0.94-1.00)	0.97 (0.94-1.01)*
Site	Larson et al., 2010 [230]	2007	Patient in care/year	Government District Hospital	8.3		
				Private company hospital	9.5		
				Mission hospital	8.9		
Care first initiated at study site	Howe et al., 2010 [226]	2001-2007	Person-months	Yes		1.00 (0.96-1.07)	1.03 (0.98-1.07)*
Need characteristics							
AIDS	Howe et al., 2010 [226]	2001-2007	Person-months	AIDS		1.17 (1.12-1.22)	1.13 (1.08-1.18)*

Group	Reference	Year(s)	Denominator	Category	Rate (95% CI)	RR (95% CI)	RR_{adj} (95% CI)
AIDS & CD4	Garattini et al., 2001 [227]	1997-1998	Person-years	ADI	5.9 (5.3-6.7)		
				no ADI, CD4 < 200	6.6 (5.1-8.6)		
				no ADI, CD4 200 - 500	6 (4.8-7.7)		
				no ADI, CD5 >500	5.6 (4.1-7.9)		
CD4	Fleishman et al., 2005 [223]	2000-2002	Calendar years	CD4 < 51	6.36-7.37		1.26 (1.21-1.31)
				CD4 51-200	6.13-6.68		1.15 (1.12-1.18)
				CD4 201-500	5.48-5.92		1.05 (1.04-1.07)
				CD4 > 500	5.07-5.33		ref
	Howe et al., 2010 [226]	2001-2007	Person-months	CD4 <200		ref	ref
				CD4 200-350		0.97 (0.92-1.03)	0.97 (0.92-1.04)*
				CD4 >350		0.90 (0.86-0.95)	0.93 (0.88-0.98)*
Viral load	Fleishman et al., 2005 [223]	2000-2002	Calendar years	Viral load < 10,000	5.50-5.94		0.97 (0.94-0.99)
				Viral load 10,000-100,000	5.58-6.04		0.98 (0.95-1.01)
				Viral load > 100,000	5.99-6.92		Ref
				Missing	2.32-2.66		0.49 (0.44-0.54)
	Howe et al., 2010 [226]	2001-2007	Person-months	Viral load <400		ref	ref
				Viral load 400-10,000		0.97 (0.92-1.01)	0.99 (0.95-1.04)*
				Viral load >10,000		0.99 (0.94-1.04)	0.99 (0.94-1.04)*

Group	Reference	Year(s)	Denominator	Category	Rate (95% CI)	RR (95% CI)	RR_{adj} (95% CI)
Anti-retroviral therapy	Cook et al., 2009 [228]	2005-2006	Annualised rate (based on 6 month periods)	No ART	4.7 (4.5-4.9)		
				Mono/dual/triple ART	6.4 (6.2-6.6)		
				Quadruple ART	8.1 (7.7-8.5)		
	Fleishman et al., 2005 [223]	2000-2002	Calendar years	No HAART	3.77-4.58		ref
				HAART	5.99-6.36		1.39 (1.36-1.42)
				Missing	5.70-6.95		1.02 (0.98-1.07)
	Bikilla et al., 2009 [229]	2003-2006	Person-years	No ART	4.6 (4.3-5.0)		
				ART	11.4 (11.0-11.7)		
	Howe et al., 2010 [226]	2001-2007	Person-months	cART		1.22 (1.15-1.28)	1.14 (1.08-1.20)*
Clinical categories & anti-retroviral therapy	Bikilla et al., 2009 [229]	2003-2006	Person-years	Non-ART, non AIDS	4.5 (4.1-4.9)		
				Non-ART, AIDS	5.9 (4.0-7.9)		
				ART, non AIDS	11.4 (11.0-11.8)		
				ART, AIDS	11.3 (10.5-12.1)		
	Paton et al., 2006 [231]	1996-2001	Person-years	CDC stage A- no ART	3.33		
				CDC stage A- Dual ART	6.69		
				CDC stage A - HAART	7.73		
				CDC stage B - no ART	5.7		
				CDC stage B - Dual ART	8.24		
				CDC stage B - HAART	7.62		
				CDC stage C - no ART	8.31		
				CDC stage C - Dual ART	9.18		
				CDC stage C - HAART	9.11		

Group	Reference	Year(s)	Denominator	Category	Rate (95% CI)	RR (95% CI)	RR_{adj} (95% CI)
Weight loss	Siddiqui et al., 2009 [224]	2005-2007	Person-years	Weight loss	9.7 (SD 12.9)		
				No weight loss	5.9 (SD 5.0)		

*RRadj also weighted for inverse probability of censoring of drop-out and death. SD standard deviation, ref reference category.

Gender

In the studies which reported utilization rates by gender, the majority of participants were male (68%-74%) [223,226,228]. Reported rates ranged between 5.46 and 6.44 visits per year [223,228].

Two of the studies (from the USA and the UK) found no significant differences in utilization rates, although unadjusted female utilization tended to be lower than male [226,228]. In contrast, the results of a repeat cross-sectional study by Fleishman et al. (2005) found utilization rates of females to be greater than males (7%-9% in each of the three years reported), with an overall significant increase of 12% found on multivariate analysis of the three year pooled data [223].

Age group

The age breakdown of participants in the three studies was broadly similar with the majority of patients being between the ages of 30 and 50 years [223,226,228]. Reported rates ranged between 4.12 and 7.4 visits per year [223,228].

All three articles reported age-groups differently, making comparisons difficult. Fleishman et al. (2005) reported three broad age categories (≤30 years, 31-49 years and 50+ years). Compared to those 30 years and under, utilization rates were 13% higher in 31-49 year olds and 27% higher in those aged 50 years and over [223].

Cook et al. (2009) reported data in five-year age bands, allowing a more detailed pattern of utilization by age emerge. They found that people in younger and older age groups had higher rates of outpatient visits than people between 20 and 39 years [228]. If their data is re-categorised into the three broad age groups reported

by Fleishman et al. (2005), the increased use in the younger age groups is masked, and a similar pattern appears (an increase of 5% and 11% in the middle and older age groups respectively).

Howe et al. (2010) did not report utilization by age group, but reported an increase of 6% in scheduled attendances with each 10 year increase in age [226].

Ethnicity

The largest group of patients in both US papers that reported ethnicity were of black ethnicity (47%-58%), with a smaller proportion (27%) of patients categorised as white [223,226]. In the UK 67% of patients were white and 27% were black Africans [228]. One of the US studies also reported a large proportion of Hispanic participants (18%-23%) [223]. Reported rates ranged between 5.1 and 7.02 visits per year [223,228].

Compared to whites, black patients tended to have fewer visits [223,226,228], but this finding was not significant in any of the studies following adjustment. In contrast, Hispanics were found to have significantly increased use compared to whites [223].

Residency/Immigrant status

The studies which reported utilization by residency/immigration status found no significant differences in utilization compared to native residents in either the UK [228] or Spain [138], with reported rates ranging between 5.2 and 6.4 visits per year.

Route of infection

Route of infection provides information on several vulnerable domains including sexual orientation and substance abuse. The categorization of risk groups varied between studies making comparisons difficult, however overall the rates of utilization varied ranged from 4.35 to 7.02 visits per year [223,228].

The most common routes of transmission were men who have sex with men (MSM) (36%-55%), followed by heterosexual acquisition (32%-38%) [223,226,228]. Heterosexuals were consistently found to have lower utilization rates than MSMs [223,226,228], although the difference was only significant in one of the studies [223].

People who had acquired their infection through injection drug use (IDU) also had slightly lower utilization rates than MSMs, with a 4% reduction on multivariate analysis of US data [223]. This was supported by data from the UK although the findings were not significant [228]. Another US study which compared IDUs to non-IDUs found IDUs to have slightly higher utilization rates, but the difference was not significant [226].

3.4.2.2 Enabling characteristics

Insurance

Two studies carried out in the US, reported utilization by insurance status, rates varied from 4.28-7.38 [223]. Both studies found uninsured patients to have fewer visits than privately insured patients on multivariate analysis, although this difference was not significant in one of the studies [226]. However, the data

regarding publically insured patients differed, with one study reporting no difference between public and no/other insurance [226], and the other reporting significant increases of 12% for Medicaid, and 22% for Medicare patients compared to those with private insurance [223].

Area of residence

The variation in categories used again made meaningful comparisons of rates difficult. One study included in this review specifically examined the relationship between rural/urban residence and use of HIV services [225]. They found utilization rates varied significantly by area of residence. Rural residents had the lowest utilization rates (3.95 visits/year), with utilization rates of urban residents and peri-urban residents being 33% (5.24 visits/year) and 11% (4.4 visits/year) higher than rural residents respectively. When restricted to patients on HAART, the difference was even greater with urban residents on HAART having utilization rates 45% (5.83 visits/year) higher than rural residents on HAART (4.02 visits/year). However, these rates were not adjusted for possible confounding variables [225].

The other studies reporting a breakdown by area of residence did not find any significant differences in utilization rates by rural/urban residence [226,228], or with distance to HIV clinic [226].

Health service resources

One study included in this review compared utilization across three sites in one province in Kenya: a government district hospital; a private company hospital; and a mission hospital [230]. All sites receive PEPFAR (US President's emergency plan for

AIDS relief) support and provide free out-patient ART. The public hospital had the lowest average number of outpatient visits per year (8.3 visits/year), while the private hospital had the highest average number of visits per year (9.5 visits/year). The differences between these rates were not tested statistically, and were not adjusted for any confounding factors. However the median baseline CD4 cell count was highest in the private hospital and lowest in the public hospital.

Source of first HIV care

Howe et al. (2010) found no difference in utilization by people who had initiated their care in their study centre compared to those had initiated their care elsewhere [226].

3.4.2.3 Need characteristics

Evaluated Health (AIDS status/CD4 count)

Five articles reported utilization rates broken down by some measure of disease severity. The individual measures used varied, however they were all based on some combination of CD4 cell count and/or clinical indicators of AIDS. Utilization rates ranged from 3.3 to 11.4 visits per year [223,227,229,231].

All studies found that as the measure of severity increased, the annual number of outpatient visits also tended to increase [223,226,227,229,231]. In studies that reported adjusted results, a clinical diagnosis of AIDS was found to be associated with a significant increase in visits (13% on multivariate analysis), and although categorization of CD4 counts varied across studies, there was a consistent and significant increase in utilization with decreasing CD4 count [223,226].

One study reported a decrease in outpatient utilization by those with most severe disease (as use of inpatient care increased) [227].

ART/HAART

The reporting of ART varied, with some studies reporting treatment (either ART or HAART) compared to no treatment [223,226,229], and others reporting levels of treatment [228,231].

In general, people on treatment tended to have more visits than patients not on treatment [223,226,228,229,231], with some evidence that utilization varied less in patients on treatment regardless of disease severity [229,231]. Two articles reported analyses adjusted for CD4 category, and both found patients on HAART attended significantly more frequently (14%–39%) than those not on HAART [223,226].

Utilization rates also vary by level of ART. In Singapore, Paton et al. (2006) found that in patients with less severe disease (CDC stage A) those on dual therapy had less frequent visits than those on triple therapy, but in patients with more severe disease (stage B and C) patients on triple therapy had lower utilization rates than those on dual therapy [231].

Cook et al. looked at quadruple therapy compared to any other ART (mono/dual/triple) and found that those on quadruple therapy have significantly more outpatient visits [228], reflecting the fact that quadruple therapy is likely to be a surrogate for HIV drug resistance and be related to an advanced and prolonged clinical history.

Viral Load

Viral load (VL) is a measure of response to therapy. Two studies reported utilization by viral load [223,226]. One of them found that utilization decreased significantly (p=0.05) as viral load decreased, but the difference was small (3% decrease in those with VL < 10,000 copies RNA/ml compared to VL > 100,000 copies RNA/ml) [223].

Other indicators of need

A study of pharmacy and claims data from a large database of commercial health plan members by Siddiqui et al. (2009) found that patients with HIV associated weight loss had significantly increased outpatient visits (9.7 visits/year) compared to those with no evidence of weight loss (5.9 visits/year) [224].

3.5 Discussion

This systematic review sought to identify determinants of HIV outpatient service utilization, using the behavioural model for vulnerable populations as an organizational framework to present and discuss the findings. The behavioural model has been used to present the results of numerous previous systematic reviews, and the use of a common framework facilitates the comparison with previously published papers across subject areas.

A review of the predictors of healthcare utilization in chronically ill populations using the behavioural model concluded that need characteristics (physical and psychological) were the strongest predictors of use, while predisposing and enabling characteristics were of little predictive value in chronically ill populations [215]. In contrast, we found that age was clearly associated with increased use of

outpatient services, with evidence from some studies that MSM acquisition, white/Hispanic ethnicity, private insurance and urban residence were also associated with increased utilization rates. The need component of the behavioural model covers both evaluated health and perceived health. As would be expected evaluated health factors (such as CD4 count and/or AIDS diagnosis) were found to be important in determining utilization patterns, with utilization increasing with severity of disease. Patients on antiviral therapy generally tend to attend clinic more frequently than people not on treatment, and their utilization rates also appear to be subject to less variation. The reasons for this are unclear, patients on treatment may simply be scheduled to visit more frequently than those not on treatment, however it is also possible that patients who attend regularly for care could be more likely to be started on treatment (i.e. health behavior influencing outcome), or alternatively, being on treatment may make patients more likely to attend care (i.e. outcome influencing subsequent healthcare use). There was a notable lack of studies on the relationship between utilization of outpatient services and perceived health.

There are several important limitations to this review. The search was restricted to four databases and to articles published in the English language. Non-peer reviewed literature, and articles that were only published in abstract form were not included. In order to allow comparability of results, studies were only included if they reported on use of hospital based HIV outpatient clinics which may limit the generalizability of the findings. In addition, the lack of information on patient outcomes and utilization of other (emergency and in-patient) services, make it

difficult to identify the health consequences, if any, associated with variation in utilization rates. The majority of studies, regardless of their design, obtained utilization data retrospectively from existing clinical or administrative databases. Retrospective database studies are a useful source of data on healthcare utilization, however there are methodological challenges associated with their use [232]. The studies included in this review generally gave little detail on the databases used, making assessment of the quality of the data sources challenging. The calculation of rates also varied between studies, limiting the interpretation of results to the relative use of services by different subgroups.

Few articles were identified that reported data outside the US and Western Europe, with only two studies from sub-Saharan Africa, one from Southeast Asia, and none from any other region of the world (e.g. Latin America, Eastern Europe/Central Asia, or East Asia). Two of the US studies reported data collected as part of the HIV Research Network (HIVRN), a consortium of sites across the US that provide primary and subspecialty HIV care, with some patient overlap possible. The purpose of the HIVRN is to obtain, analyse and disseminate data on HIV service utilization in order to provide information for planning and quality assessment of HIV services in the US [233]. No equivalent source of information exists in any other region of the world however, and extrapolation from US data to other regions is difficult, as the structures of healthcare systems as well as the patients cohorts differ considerably. Differences in the categorization of subgroups reported also made comparisons across studies difficult, and can influence the actual rates reported (as was illustrated by the differing age categorizations [223,228]. Future publications should

look to the literature to inform their choice of subgroups, and should report as detailed a breakdown as is practicable, preferably including raw numbers so that if needed, rates could be recalculated for different categorizations.

While little can be concluded about the absolute visit rates reported (Table 3-4), it is worthwhile noting that the rates were of a similar magnitude across all studies (possibly a reflection of the inclusion criteria for this review), and interestingly, virtually all groups had rates above 4 visits/year, i.e. all groups appear to attend at least as frequently, on average, as is recommended in international guidelines. It is likely that the inclusion criteria of individual studies means that these rates are for people actively engaged in care and have, intentionally or unintentionally, excluded poor attenders which would reduce the averages. In any case, average rates may not by the most appropriate measure of visit data as the data are likely to be very skewed and may be influenced by a minority of high-frequency users (e.g. newly diagnosed/starting or switching treatment). Previous studies have identified subgroups of patients who do not attend as regularly as recommended and/or who have higher missed-appointment rates [76,234,235] but this was not reflected in the results of this review. As previously mentioned, this could be a consequence of the inclusion criteria of individual studies, or could be a result of looking at average rates as opposed to proportional measures. At the other end of the spectrum, many groups appear to be attending well in excess of the recommended frequency, although again, due to the limitations of this review the reasons behind this cannot be elucidated.

This review has identified several factors which influence use of HIV services and which should be considered when developing future models projecting the future burden or cost of care for people living with HIV. The increased use of HIV out-patient services associated with older age groups described in this review is consistent with the reported increase in prevalence of co- and multi-morbidity in older HIV patients [236,237]. As the proportion of older HIV patients rises, the increasing prevalence of co- and multi-morbidity means that demands on health services will multiply accordingly. Anticipating future demands is an essential part of healthcare planning, ensuring adequate provision and allocation of whatever resources are available to provide the most efficient and effective health service possible. In the case of HIV, models predict not only an increase in the total number of patients, but also substantial increases in the proportion of older patients, and in the numbers of patients requiring second-line and subsequent therapies in the coming years [195]. The resource implications of these changes are considerable, not only for the HIV services themselves, but also for the other chronic disease (e.g. oncology [169], cardiac [238], renal [239], and transplant services [170,240]) and geriatric care [172] specialties that will be seeing more and more HIV-infected patients, and for the co-ordination of care across these multiple providers.

While the changing age profile of HIV patients is the most obvious, and probably the most important factor, several of the other factors are also likely to change in the future, for example increasing health insurance coverage as a result of the affordable health care act in the USA [241], and increasing levels of urbanization [242]. Modelling studies estimating the future cost/burden of HIV should at least

consider the possible effects that changing patient, health service and societal changes could have on service use in the future. To date, estimates have been based on current rates of service usage, and have only taken clinical factors, such as severity and ART into account [142,243]. This review has also highlighted several areas, including patient outcomes, health beliefs and treatment status, where specific research is needed to elucidate their relationship with utilization of outpatient services. Further work on the relationship between patient outcomes and utilization of outpatient services could shed some light on what constitutes under- and over-utilization. Research examining the role of health beliefs in utilization may provide useful insights for the development or implementation of patient engagement interventions. Information on the direction and magnitude of the relationship between treatment and utilization may also provide insights into the possible role of treatment as a tool for improving engagement, but is also needed to estimate potential increases in service demand as the numbers of people on treatment increase.

In conclusion, several factors were found to be associated with utilization of outpatient HIV services. As the HIV epidemic evolves these factors may play an increasing role in the demands placed on HIV services, and the most important factors need to be identified and taken into account in future modelling and/or cost-effectiveness studies.

In terms of the relevance of the results of this literature review to the overall thesis, this review was performed in order to identify important patient and/or healthcare characteristics associated with use of outpatient HIV services to inform the

variables collected as part of the costing studies reported subsequently in this thesis. Possibly due to the small number of articles meeting the inclusion criteria, the differing time periods of the studies included and/or the differences in healthcare systems across jurisdictions this review did not identify any variables which were clearly associated with use of outpatient services, relevant to an Irish context, other than those which would have been included anyway as part of the basic patient demographic and clinical data (e.g. age, CD4 count, treatment status, suppression status etc).

4 Resource utilisation and cost of ambulatory HIV care in a regional HIV centre in Ireland: A micro-costing study

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This paper was published in BMC Health Services Research in 2015 (See Appendix 1)

4.1 Abstract

Background

It is anticipated that demands on ambulatory HIV services will increase in coming years as a consequence of the increased life expectancy of HIV patients on HAART. Accurate cost data are needed to enable evidence based policy decisions be made about new models of service delivery, new technologies and new medications.

Methods

A micro-costing study was carried out in an HIV outpatient clinic in a single regional centre in the south of Ireland. The costs of individual appointment types were estimated based on staff grade and time. Hospital resources used by HIV patients who attended the ambulatory care service in 2012 were identified and extracted from existing hospital systems. Associations between patient characteristics and costs per patient month, in 2012 euros, were examined using univariate and multivariate analyses.

Results

The average cost of providing ambulatory HIV care was found to be €973 (95% confidence interval €938-€1,008) per patient month in 2012. Sensitivity analysis, varying the base-case staff time estimates by 20% and diagnostic testing costs by 60%, estimated the average cost to vary from a low of €927 per patient month to a high of €1,019 per patient month. The vast majority of costs were due to the cost of HAART. Women were found to have significantly higher HAART costs per patient

month while patients over 50 years of age had significantly lower HAART costs using multivariate analysis.

Conclusions

This study provides the estimated cost of ambulatory care in a regional HIV centre in Ireland. These data are valuable for planning services at a local level, and the identification of patient factors, such as age and gender, associated with resource use is of interest both nationally and internationally for the long-term planning of HIV care provision.

4.2 Background

The availability of effective treatment since the mid-1990s, has transformed HIV infection into a chronic disease [244]. Nowadays, with timely diagnosis and engagement in care, people living with HIV can have a life-expectancy that approaches that of the general population [9,208]. However, HAART is not a curative treatment and most newly diagnosed HIV patients face the daunting prospect of decades of medication use and regular healthcare visits. It has also become apparent that long term HIV infection and medication use is associated with increased non-AIDS morbidity [24,244,245].

Since HIV testing began in the early 1980s over 6,600 people have been diagnosed with HIV in Ireland [246]. A prevalence study of patients in care found 3,254 patients accessed HIV care in Ireland in the 12-month period from July 2009 to June 2010, with 25% over 45 years of age [247]. Of these patients, 80% were on treatment and 94% of those had a viral load < 500 copies/ml [85], figures that compare favourably with other developed countries [248-250]. In Ireland, as in many other countries, policy makers and clinicians are now faced with the challenge of continuing to provide high quality care in the context of increasing demand and within on-going financial constraints.

Data on the use and cost of services are needed to estimate the potential impact the changing HIV epidemiology will have on the health service in Ireland, as well as to support evidence based decisions about new models of service delivery, technologies and medications [251]. It is not generally appropriate to extrapolate

costs from studies in different countries due to variation in how health services are provided and organised.

There are two general approaches to costing healthcare: top-down and bottom up. A top-down approach estimates the cost of an individual service on average, usually using routinely available data e. g. average *per diem* costs. Top-down costing studies tend to be relatively quick and easy to carry out, however they are also less precise and cannot provide information on individual factors driving the costs [252]. A bottom-up approach (micro-costing) generates a more precise estimate, but is more difficult to perform. In micro-costing all resources used are identified and then the unit costs of the resources are multiplied by the quantities used [252]. Studies examining the differences between the cost estimates produced by the two approaches have concluded that bottom-up approaches are preferable for estimating cost components which have a large impact on total costs (e.g. labour, drugs), for services where there is wide variation in costs between patients and for centres which are integrated within a larger hospital compared to stand-alone centres [253-255].

Existing data on the cost of outpatient care in Ireland are limited. The national average cost of an outpatient visit in Ireland was estimated to be €130 in 2011 using a top-down methodology [256], however no information is available on how this cost may vary across specialties. A previous study looking specifically at the pharmacoeconomics of HIV in Ireland carried out in the early HAART era reported an average outpatient cost of IR£493 per active patient month in 1999 which would

be equivalent to €1,184 in 2012 (inflated using the Irish consumer price index for health) [143,257].

Ireland is currently in the process of restructuring its healthcare funding system from one where hospitals are funded based on historical levels of funding adjusted for activity and patient mix to a prospective case based payment system ("Money Follows the Patient") [258]. While it is initially planned to implement this change for in-patient and day-case activity, the new funding system will also encompass outpatient services [258]. It is proposed that prices in the new system will be set initially with reference to average prices, but with a view to implementing best practice prices on an incremental basis [258].

The aim of this study was to estimate the total cost of providing an outpatient HIV service in a single centre in 2012 from the health service provider perspective, and to identify associated patient factors. We also compare our results with other available sources of cost data.

4.3 Methods

Ethics

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of CUH.

Description of service

CUH is one of the largest university teaching hospitals in Ireland, and provides HIV care for the counties of Cork, Kerry, Waterford, and South Tipperary (covering approximately 20% of the Irish population). The ID department holds two routine outpatient clinics specifically for HIV patients: the main HIV clinic ("HIV clinic") held

once a week and a joint ID-maternity clinic ("antenatal-HIV clinic") held once a month in the adjoining maternity hospital. Patients attending the antenatal-HIV clinic attend both obstetric and ID services during their appointment.

Local clinical guidelines, based on international best-practice [3,41,42], recommend that a CD4 count, viral load (VL), full blood count (FBC) and biochemistry patient profile (renal, liver and bone profiles) are performed every 3-4 months. Additional and/or more frequent testing is recommended at initiation of care and at initiation of HAART until suppression is achieved. Antenatal HIV patients are monitored on a monthly basis.

Study participants

All patients who attended for HIV care in 2012 were identified from a pre-existing clinical database which contains the results of all viral load tests performed in CUH. The database also contains basic demographic and risk factor information on the patients who have attended the public HIV clinic in CUH. Patients who attended the public HIV clinic at least once in 2012 were eligible to be included in the study. Patients who attended for private HIV outpatient care, who did not attend any outpatient appointment in 2012, or who routinely attended another HIV centre for their HIV care were excluded.

For new patients to the clinic in 2012 (newly diagnosed or transferred from another clinic) the date of their first appointment attended or admission was taken as the start date of their care, for all other patients the start date of care was 01/01/2012. Patients were considered to be in care until 31/12/2012 if they used any hospital service (outpatient/in-patient/emergency department) at least once between

01/07/2012 and 31/12/2012. The files of patients who did not use any hospital service in the last 6 months of 2012 were manually checked, and these patients were censored at the date of their last scheduled appointment where appropriate. Patients who had either a CD4 count < 350 cells/μl or an AIDS defining illness at the time of diagnosis recorded in their medical notes were categorised as late diagnoses.

Resource use

Information on the number and dates of all outpatient appointments and diagnostic tests (laboratory, radiology and cardiology) were extracted from the hospital information system. Data on the total number of months of each HAART regimen dispensed, as well as any relevant start and/or stop dates, were extracted from pharmacy patient files. The medical records of patients with no pharmacy files were cross-checked to confirm the patient did not receive HAART in 2012. In addition, information on the number of doses of prophylactic antibiotics (azithromycin, dapsone, sulfamethoxazole/trimethoprim and pyrimethamine) dispensed to HIV patients was provided by the hospital pharmacy. Diagnostic tests were linked with patient appointments on the basis of matching test and appointment dates. Radiology and cardiology tests, which may not occur on the date of the outpatient appointment where the test was ordered, were linked with the nearest previous outpatient appointment attended.

Costs

A micro-costing study was carried out to estimate the cost of typical HIV outpatient appointments from the service-provider perspective in 2012. Staff routinely

involved in providing or supporting the HIV clinic (clerical, nursing, medical, phlebotomy, and pharmacy) were interviewed to assess the HIV-clinic related tasks performed by the staff member and the estimated patient-facing and non patient-facing time involved. Doctors and nurses self-recorded their patient-facing times at six consecutive HIV clinics in March and April 2013 (127/153 appointments timed). Pharmacy staff self-recorded their HIV related patient-facing and non patient-facing time for the month of April, 2013. The accuracy of self-timed doctor patient-facing times was confirmed by independent observation of approximately 50% of appointments. Average costs per appointment were then calculated based on estimated time and salary of relevant staff using recommended national guidelines [259,260].

The total annual staff cost per grade was calculated as follows:

Pay = Mid-point of pay range

Direct Salary Cost = Pay + Employers PRSI (10.75%)

Total Salary Cost = Direct Salary Cost + Imputed Pension Cost (4% of Pay)

Total Staff Cost = Total salary cost + Overheads (25% of Pay)

This method includes adjustments for non-pay costs associated with hiring additional staff including employers' PRSI, superannuation, as well as general overheads such as costs for accommodation, utilities, support and back-office staff, training, travel etc [259]. Total staff cost was converted to hourly rates using the formula: annual cost for grade/((249- annual leave entitlement) x 6.95)) [259].

Eight basic types of appointment were identified: 1) did not attend scheduled outpatient appointment (DNA), patient was not on HAART at the time ("DNA, not on HAART"); 2) DNA, patient was on HAART at the time ("DNA, on HAART"); 3) attended the HIV-clinic, patient was not on HAART at the time ("Attended HIV clinic, not on HAART"); 4) attended the HIV-clinic, patient was on HAART at the time ("Attended HIV clinic, on HAART"); 5) attended the antenatal HIV-clinic, patient was not on HAART at the time ("Attended antenatal-HIV clinic, not on HAART"); 6) attended the antenatal-HIV clinic, patient was on HAART at the time ("Attended antenatal-HIV clinic, on HAART"); 7) first attended appointment with the ID service for HIV care, patient was not on HAART at the time ("Baseline visit, not on HAART"); and 8) first attended appointment with the ID service for HIV care, patient was on HAART at the time ("Baseline visit, on HAART"). Appointments were categorised as DNA if the patient did not attend their scheduled appointment without cancelling or rescheduling the appointment prior to the start of the clinic they were due to attend. The cost of a DNA appointment was estimated based on the same non patient-facing administrative and pharmacy staff time (where applicable) as attended appointments as well as the time incurred rescheduling an appointment. In general, a patient is considered lost to follow-up if they DNA three consecutive appointments. For the antenatal-HIV clinic appointments only the cost of the care delivered by the ID team was included in the micro-costing.

Unit costs

The unit costs of diagnostic tests were obtained from the finance department of the hospital and the National Virus Reference Laboratory. The monthly costs of ARVs and prophylactic antibiotics were provided by the hospital pharmacy. In Ireland, the

price of all prescribed drugs are set at a national level [261,262], although individual hospitals can negotiate discounts with wholesalers. The number of months of regimens dispensed was used in the calculation of HAART costs to allow for possible wastage due to regimen switching.

The hospital finance department also provided outpatient costs per patient for comparison purposes from a newly implemented activity based costing system. These data were broken down into direct and indirect costs by category (clinical salaries, nursing salaries, non-clinical salaries, imaging, pathology etc), but contained little information on individual patient characteristics, appointment types or diagnostic tests. Drug costs (with the exception of a few very high cost drugs) were not assigned at a patient level in the hospital activity based costing system in 2012.

The unit costs of individual appointment types, common diagnostic tests and regimen types are shown in Table 4-1.

Table 4-1. Unit costs (in 2012 euros) and frequency of appointment types, most common diagnostic tests and most common HAART regimens dispensed.

Cost category	Unit cost	Resource use	Source of cost data
Appointment type	*Staff cost/ appointment*	*Number of appointments*	
DNA, not on HAART	€12.68	32	Micro-costing study
DNA, on HAART	€21.25	127	Micro-costing study
Attended HIV clinic, not on HAART	€174.89	89	Micro-costing study
Attended HIV clinic, on HAART	€194.88	997	Micro-costing study
Attended antenatal-HIV clinic, not on HAART	€174.26	2	Micro-costing study
Attended antenatal-HIV clinic, on HAART	€194.25	42	Micro-costing study
Baseline appointment, not on HAART	€244.46	14	Micro-costing study
Baseline appointment, on HAART	€264.45	12	Micro-costing study
Most common diagnostic tests	*Cost per test*	*Number of tests*	
CD4	€47.29	1,013	Hospital Finance Dept
Viral load	€92.94	995	National Virus Reference Laboratory
Full Blood Count	€6.79	1,036	Hospital Finance Dept
Biochemistry profiles, weighted average cost	€18.63	1,042	Hospital Finance Dept
All other tests, weighted average cost	€28.39	1,262	Hospital Finance Dept
HAART regimens (regimen class)	*Cost per month*	*Number of months dispensed*	
Efavirenz/Emtricitabine/Tenofovir (NNRTI)	€816.61	1,515	Hospital pharmacy
Emtricitabine/Tenofovir, Darunavir, Ritonavir (PI)	€1,097.51	864	Hospital pharmacy
Emtricitabine/Tenofovir, Atazanavir, Ritonavir (PI)	€1,084.84	389	Hospital pharmacy
Emtricitabine/Tenofovir, Lopinavir/Ritonavir (PI)	€1,148.79	99	Hospital pharmacy
Emtricitabine/Tenofovir, Nevirapine (NNRTI)	€747.98	75	Hospital pharmacy
Lamivudine/Zidovudine, Lopinavir/Ritonavir (PI)	€953.16	53	Hospital pharmacy
All other regimens, weighted average cost	€923.70	327	Hospital pharmacy
Prophylactic antibiotics	*Cost per dose*	*Number of doses dispensed*	
Azithromycin	€0.42	330	Hospital Pharmacy
Sulfamethoxazole and trimethoprim	€0.15	2,047	Hospital Pharmacy
Dapsone	€0.69	344	Hospital Pharmacy

DNA, did not attend. “Staff cost” is the estimated total patient and non patient-facing staff costs per appointment. Diagnostic tests includes laboratory, radiology and cardiology tests. “Biochemistry profiles” refers to the number and weighted average cost of the following biochemistry profiles: “patient”, “ward”, “bone”, “renal/bone”, “patient & lipid”, “patient & lipoprotein”, “urea, electrolytes & creatinine” and “liver function tests”.

Data analysis

All information was entered into a Microsoft Access® database. Data were analysed using Microsoft Excel® and STATA 12 (College Station, Texas). Weighted average costs per patient month (ppm) were calculated to account for differences in patient lengths of follow-up. χ^2 tests were used to test for differences in proportions. Logistic regression was used to estimate the odds ratios of being treated with PI-based regimens compared to NNRTI-based regimens in patients receiving a single type of regimen. Generalised linear models were used to model costs ppm on HAART as they are suitable for modelling cost data, which tend to be skewed, without the need for transformation [263]. The most appropriate family was chosen using the modified Parks test, and the link was chosen using the Pearson Correlation Test, the Pregibon Link Test and the modified Hosmer and Lemeshow test to evaluate power links in increments of 0.1 between 0 and 1 [264].

Sensitivity analysis

To reflect the uncertainty in the estimates of staff time and laboratory costs staff times were varied by 20% and unit costs of diagnostic testing by 60% in a sensitivity analysis. The 20% variation in staff time was based on the approximate width of the confidence intervals of the average doctor and nurse patient-facing times, while the choice of 60% variation for diagnostic testing costs was based on the difference in the weighted average test costs calculated using alternative unit costs which were available for a limited number of the tests.

4.4 Results

4.4.1 Study population

In total 326 patients (3,659 patient months) were included in this study. The characteristics of the patient population can be seen in Table 4-2. The majority of patients (59%) were men and the average age of patients was 40 years. Co-infection with hepatitis C virus (HCV) was recorded for 7% of patients, Hepatitis B Virus (HBV) in 2% of patients and both HBV and HCV in 1% of patients. Eight percent (26/326) of patients were new to the service in CUH in 2012, most of whom were newly diagnosed in 2012 (n=17). The CD4 profile of patients improved with the number of years since diagnosis (χ^2 test, P=0.001).

Three patients died in 2012, two of these were considered HIV-related deaths both of which were of people who were newly diagnosed with advanced illness (CD4 < 50 cells/µl) at the time of diagnosis.

Table 4-2. Number and proportion of patients and patient-months by patient characteristics

Characteristics		Patients (%)	Patient months (%)
Patient type	Existing patient	300 (91%)	3,506 (95%)
	New patients	26 (8%)	153 (4%)
Gender	Male	192 (59%)	2,148 (58%)
	Female	134 (41%)	1,511 (41%)
Age	<50 years	284 (87%)	3,172 (86%)
	50+ years	42 (13%)	487 (13%)
Risk factor	COHP	133 (41%)	1,501 (41%)
	Heterosexual	63 (19%)	721 (20%)
	MSM/Bisexual	95 (29%)	1,067 (29%)
	IDU	18 (5%)	185 (5%)
	Other	8 (2%)	96 (3%)
	Unknown	9 (3%)	89 (2%)
Late diagnosis	No	135 (41%)	1,535 (42%)
	Unknown	77 (23%)	840 (23%)
	Yes	114 (35%)	1,284 (35%)
Years since diagnosis	11+ years ago	95 (29%)	1,107 (30%)
	6-10 years ago	107 (33%)	1,231 (34%)
	1-5 years ago	100 (30%)	1140 (31%)
	diagnosed in 2012	17 (5%)	105 (3%)
Lowest CD4 count in 2012 (cells/µl)	500+	168 (51%)	1,894 (52%)
	350-499	85 (26%)	973 (26%)
	200-349	52 (16%)	581 (16%)
	50-199	14 (4%)	146 (4%)
	<50	7 (2%)	65 (2%)
Treatment and viral load status[b]	On HAART, suppressed	211 (64%)	2,469 (67%)
	On HAART, not suppressed	37 (11%)	438 (12%)
	On HAART, unable to determine status	7 (2%)	75 (2%)
	Started/Stopped HAART	49 (15%)	440 (12%)
	Not on HAART	22 (7%)	237 (6%)
Overall		**326 (100%)**	**3,659 (100%)**

4.4.2 Resource use

There were a total of 1,315 HIV outpatient appointments scheduled during 2012, with an average of 4.1 (median 4, range 1-15) scheduled appointments per patient

and 3.6 (median 3, range 1-11) attended appointments per patient. The frequencies of each type of appointment are shown in Table 4-1.

In total 304 patients were on HAART for 3,272 patient-months, with 3,322 months of HAART dispensed in total. The majority of regimens dispensed consisted of a nucleoside reverse-transcriptase inhibitor (NRTI) backbone combined with either a protease inhibitor (PI) or a non-nucleoside reverse-transcriptase inhibitor (NNRTI). NNRTI-based regimens were the most frequently dispensed (164 patients, 1,755 months dispensed) followed by PI-based regimens (145 patients, 1,477 months dispensed), with a small number of patients being dispensed other regimens types (10 patients, 90 months dispensed). Fifteen percent (n=45) of patients had more than one regimen prescribed during the study period, most of which were within the same class, although a small number of patients were prescribed regimens from different classes during the study period (n=15).

4.4.3 Total costs

The overall average cost of providing HIV outpatient care was estimated to be €973 ppm in 2012 (median €940, interquartile range €938-€1,008). As the cost of HAART accounted for the majority (88%) of total costs, varying the staff time estimates and unit costs of diagnostic testing did not result in substantial changes to the average costs ppm in the sensitivity analysis, with total costs ppm only varying by about 5% (Table 4-3). When costs were stratified by whether the patient was on HAART or not at the time, the average cost ppm not on HAART was €107 (95% CI €65-€150) compared to €1,085 (95% CI €1,060-€1,111) ppm on HAART.

Table 4-3. Average base-case cost, in 2012 euros, per patient month (ppm) and results of sensitivity analysis.

	Base case (95% CI)	Lower estimate (95% CI)	Upper estimate (95% CI)
Staff costs ppm (+/- 20%)	€62 (€59-€65)	€50 (€47-€52)	€75 (€71-€78)
Diagnostic test costs ppm (+/-60%)	€55 (€52-€59)	€22 (€21-€23)	€89 (€83-€94)
Total non-drug cost ppm	**€117 (€111-€124)**	**€72 (€68-€76)**	**€163 (€154-€172)**
Total cost ppm (including drug costs)	**€973 (€938-€1,008)**	**€927 (€893-€962)**	**€1,019 (€983-€1,054)**

4.4.4 Patient factors

The mean total cost ppm generally differed little across patient groups (Table 4-4). However, patients who were on HAART for the duration of their time in the study and were categorised as suppressed were found to have lower average total monthly costs compared to those who were not suppressed (mean €1,043 ppm compared to €1,189 ppm respectively).

HAART accounted for the vast majority of outpatient costs. The unit cost of individual regimens varied from a minimum of €552/month to a maximum of €1,600/month. Although NNRTI-based regimens tend to be less expensive than PI-based regimens (the weighted average cost of NNRTI-based regimens in this study was €809/month compared to €1,091/month for PI-based regimens), there are many other factors apart from cost which influence regimen choice, including patient (e.g. demographic, behavioural), clinical (resistance, adverse reactions, co-morbidities) and health system factors (drugs available for prescription, clinician preferences). Significantly lower proportions of new patients and newly diagnosed patients received HAART in 2012 compared to existing and previously diagnosed patients (χ^2 test, P=0.008 and P=0.017, respectively). While a significantly higher proportion of those diagnosed late (i.e. with a CD4 count <350 cells/µl or an AIDS

defining illness at diagnosis) received HAART (χ^2 test, P=0.003). On multivariate logistic regression of these three factors late diagnosis was the only factor that remained significant with an odds ratio (OR) of 15.5 (95% CI 2-120). Logistic regression of regimen type (analysis restricted to patients only prescribed PI-based regimens or only prescribed NNRTI-based regimens, n=283) found women were significantly more likely to be prescribed a PI-based regimen (OR 6.6, 95% CI 3.3-13.2, p<0.001), while those over 50 years were less likely to be prescribed a PI-based regimen (OR 0.34, 95% CI 0.14-0.85, p=0.022) when adjusted for risk factor, patient type, years since diagnosis, CD4 <350 cells/µl and late diagnosis.

The cost of HAART is the main driver of total costs, so any analysis of the factors associated with total costs in effect just identifies the factors associated with HAART cost. In order to try and identify the factors associated with outpatient service use multivariate analyses was carried out separately on the non-HAART costs, the HAART costs and the total cost ppm on HAART (3,272 patient months). The results of these multivariate analyses are shown in Table 4-5. Female patients were significantly more expensive compared to male patients and patients who were not suppressed were more expensive compared to those who were suppressed, reflecting the fact that more expensive PI-based regimens were more commonly dispensed in these groups of patients (67% months of HAART dispensed to females were PI based regimens vs 30% of months dispensed to males, and 61% of months of HAART dispensed to patients on HAART not suppressed/other vs 37% of months dispensed to suppressed patients). Patients over aged ≥50 years on the other hand had significantly decreased total costs ppm on HAART compared to

patients under 50 years of age, again reflecting the regimens used in these groups (50% of months of HAART dispensed to patients <50 years were NNRTI-based regimens vs 72% of months dispensed to those ≥50 years).

In terms on non-HAART costs, older patients had significantly lower non-HAART costs ppm on HAART, while patients diagnosed between 1 and 5 years ago were more expensive than those diagnosed more than 10 years previously, and patients who had a CD4 count < 350 cells/µl were more expensive than those with a higher cell count.

Table 4-4. Costs per patient month (ppm) by patient subgroup

	N	Mean drug cost ppm (95% CI)	Mean non-drug costs ppm (95% CI)	Mean total cost ppm (95% CI)
Patient type				
Existing patient	300	€863 (€829-€897)	€112 (€107-€116)	€975 (€940-€1,010)
New patients	26	€678 (€503-€853)	€253 (€206-€300)	€931 (€732-€1,130)
Gender				
Male	192	€844 (€805-€882)	€117 (€109-€124)	€960 (€921-€999)
Female	134	€873 (€812-€934)	€118 (€108-€129)	€991 (€927-€1,055)
Age group				
<50 years	284	€859 (€821-€897)	€121 (€114-€128)	€980 (€941-€1,019)
50+ years	42	€833 (€773-€894)	€94 (€85-€104)	€928 (€871-€984)
Risk factor				
COHP	133	€878 (€826-€931)	€117 (€106-€127)	€995 (€940-€1,050)
MSM/Bisexual	95	€826 (€769-€884)	€122 (€110-€134)	€948 (€889-€1,007)
Heterosexual	63	€835 (€745-€925)	€113 (€101-€125)	€948 (€856-€1,041)
IDU	18	€931 (€834-€1,027)	€124 (€103-€144)	€1,054 (€942-€1,166)
Other	8	€982 (€733-€1,231)	€92 (€59-€125)	€1,075 (€817-€1,332)
Unknown	9	€697 (€383-€1,012)	€125 (€92-€159)	€823 (€514-€1,132)
Late diagnosis				
No	135	€810 (€748-€871)	€120 (€111-€130)	€930 (€867-€993)
Unknown	77	€868 (€797-€939)	€115 (€103-€126)	€983 (€908-€1,058)
Yes	114	€902 (€862-€942)	€116 (€104-€127)	€1,018 (€974-€1,062)

	N	Mean drug cost ppm (95% CI)	Mean non-drug costs ppm (95% CI)	Mean total cost ppm (95% CI)
Years since diagnosis				
11+ years ago	95	€879 (€830-€929)	€102 (€95-€108)	€981 (€930-€1,032)
6-10 years ago	107	€890 (€833-€947)	€107 (€99-€115)	€997 (€938-€1,056)
1-5 years ago	100	€831 (€762-€899)	€130 (€119-€141)	€961 (€889-€1,033)
diagnosed in 2012	17	€581 (€349-€812)	€275 (€208-€342)	€855 (€582-€1,128)
Lowest CD4 count in 2012 (cells/µl)				
500+	168	€888 (€844-€932)	€104 (€98-€110)	€993 (€947-€1,038)
350-499	85	€807 (€734-€879)	€120 (€108-€132)	€927 (€852-€1,002)
200-349	52	€830 (€735-€925)	€129 (€114-€145)	€960 (€861-€1,058)
50-199	14	€839 (€725-€953)	€179 (€115-€244)	€1,018 (€873-€1,164)
<50	7	€903 (€706-€1,100)	€218 (€118-€319)	€1,121 (€842-€1,401)
Treatment and viral load status				
On HAART, suppressed	211	€939 (€915-€964)	€104 (€100-€109)	€1,043 (€1,017-€1,069)
On HAART, not suppressed	37	€1,035 (€987-€1,083)	€154 (€134-€175)	€1,189 (€1,133-€1,245)
On HAART, undetermined status	7	€914 (€776-€1,052)	€84 (€55-€113)	€998 (€845-€1,151)
Started/Stopped HAART	49	€660 (€578-€742)	€169 (€141-€197)	€829 (€733-€924)
Not on HAART	22	-	€103 (€79-€128)	€103 (€79-€128)
Overall	**326**	**€856 (€822-€889)**	**€117 (€111-€124)**	**€973 (€938-€1,008)**

COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/µl at diagnosis or AIDS defining illness at diagnosis. "On HAART" means the patient was on HAART for the entire duration of the study, "suppressed" was defined as all viral loads in 2012 <50 copies/ml, with one test result of 50-499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml.

Table 4-5. Results of multivariate analysis of non-HAART, HAART and total costs ppm on HAART.

	Non HAART cost ppm on HAART Coefficient[1]	HAART cost ppm Coefficient[2]	Total cost ppm on HAART Coefficient[2]
New patient	-6.555	-0.03	-0.004
Female	1.464	0.138*	0.139*
Age 50+ years	-3.113*	-0.101*	-0.117*
Risk factor			
COHP	ref	ref	ref
MSM	1.308	0.033	0.037
Heterosexual	0.32	0.054	0.054
Other/unknown	-0.737	0.05	0.054
Late diagnosis			
No	ref	ref	ref
Unknown	-0.354	-0.012	-0.015
Yes	-0.515	-0.035	-0.04
Years since diagnosis			
11+ years ago	ref	ref	ref
6-10 years ago	-0.267	0.053	0.05
1-5 years ago	1.825*	0.041	0.059
diagnosed in 2012	4.504	0.078	0.128
Min CD4 < 350 cells/µl	3.432*	0.02	0.054
On HAART, not suppressed/other	2.051	0.059	0.089*
Constant	31.314	3.896	4.026

1) Generalised linear model with Inverse Gaussian family and link power 0.5. 2) Generalised linear model, with Gaussian family and link power 0.2. * p<0.05. PPM, per patient month. COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/µl at diagnosis or AIDS defining illness at diagnosis. "On HAART" means the patient was on HAART for the entire duration of the study, "suppressed" was defined as all viral loads in 2012 <50 copies/ml, with one test result of 50-499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml. "On HAART, other" includes patients on HAART who were not suppressed or had undetermined status and those who started/stopped HAART in 2012.

4.4.5 Comparisons of total costs with other sources of cost data

Patient level costs for the HIV patients included in the micro-costing study were provided by the hospital finance department. The data are activity based costing data, the cost components of which are generated using a top-down methodology. The total number of HIV outpatient appointments in the finance dataset was very similar to the total scheduled number of appointments from the utilisation study (1,310 vs 1,315) which would be expected given that the finance costs are based on information recorded in the same hospital information system as the utilisation data were extracted from. As the costs of most drugs were not assigned at a patient level in this system in 2012, it was not appropriate to compare drug costs, however the estimated non-drug cost ppm based on the hospital activity-based cost data was €63 ppm (95% CI €59-€67) compared to €117 (95% CI €111-€124) in the micro-costing study. Use of the national average outpatient appointment cost (€130.56 in 2012) would have resulted in an even lower estimate of €47ppm (95% CI €44-€49ppm). While our estimate is greater than the estimates generated using routine data, the estimated total cost (€973 ppm) is about 20% lower than the IR£493 per active patient month in 1999 reported by a previous micro-costing study (equivalent to €1,184 in 2012). Although that study was carried out in the early HAART era and the patient population was quite different to the patient population in this study [143].

4.5 Discussion

This study reports the results of a bottom-up costing study of routine HIV outpatient care performed in a regional referral centre in the south of Ireland. The total estimated cost of the service in 2012 was €973 ppm, nearly 90% of which was

due to the cost of HAART. While it is difficult to compare costs across countries, HAART is reported to account for 60%-80% of the total cost of HIV care (including inpatient care) in many studies in developed countries [121,128,134,265-268].

Despite its cost, HAART is considered a very cost-effective treatment [117,269], and also has the important population-level benefit of reducing onward transmission [270]. HAART also offers the greatest opportunity for reducing costs, for example, in this study the total non-drug spend would have to be reduced by over 35% to save the same amount as could be achieved by a 5% reduction in HAART costs. Possible strategies for reducing HAART costs do exist, such as increased use of generic drugs or less expensive regimens where available and appropriate [119,127,159], though efforts to reduce drug spend should not come at the cost of increased risk of poorer outcomes and reduced quality of care [269]. As regimen choice is influenced by patient factors, such as age, gender and risk factor, variation in costs between centres at a national level is likely to be a reflection of differences in patient populations, although clinician preference may also play a role. With time, as more patients switch onto newer treatments, the drug costs are likely to increase unless savings can be made through increased use of generic drugs [119,127,159] or other rationalisation measures. In any case, further research is warranted into the patient and healthcare factors influencing regimen choice, such as the acceptability and potential impact of a preferred medicine scheme.

The most important factor on multivariate analysis which influenced total costs ppm on HAART was gender, with women being 15% more expensive than men. It was also interesting to note that patients over 50 years of age had significantly

reduced costs ppm on HAART. This was due to a combination of older patients tending to be on less expensive NNRTI-based regimens, as well as having fewer scheduled appointments (0.26 ppm compared to 0.37 ppm, $p<0.001$). The lower appointment rate in older patients contrasts with previous studies which have found older patients have higher utilisation rates [271], and may be a reflection of the particular characteristics of this patient cohort. As the total number of older patients increase, it will be possible to perform more nuanced analysis by age, which may identify particular age groups with higher resource use (e.g. 50-65 year, 65-75 year, 75+ year age groups). Late diagnosis has been reported in the literature to be associated with sustained increased healthcare costs [133], in this study there was some evidence that those diagnosed late had higher mean outpatient costs (Table 4-4), however the differences were not significant using multivariate analysis.

There are several limitations to this study. The data collection was restricted to one year, so changes over time cannot be examined. The usage and cost of other services (inpatient, emergency, and non-ID outpatient care) were not included in this analysis. While the majority of HIV-related care is now provided on an out-patient basis by the ID team, a small minority of patients use a substantial amount of other services [272]. Newly diagnosed patients with low CD4 counts in particular can have very complex care needs, in this study the inpatient costs of two newly diagnosed patients who were diagnosed late and subsequently died were not captured by this micro-costing study. CUH has a smaller proportion of injecting drug users than the national HIV patient population (5% vs 21%), however the population served is similar in terms of age, gender, CD4 count and viral load to the

national cohort in care [247]. Diagnostic tests were linked to specific outpatient appointments on date and mis-matching may have occurred which could have led to either an under- or over-estimate of the diagnostic testing ordered by the HIV clinic. Private patients were not included in the study. While private patients do not attend the public outpatient clinic so would not generate appointment costs, the health service provider may incur costs as a result of diagnostic tests and/or HAART. The additional cost of obstetric care for HIV patients (i.e. additional to the three consultant visits that antenatal patients are routinely entitled to [273]) was not included in the cost estimates. As the numbers of women attending antenatal care was very small in this study it was not possible to investigate this fully, but to give an indication of the scale of the possible additional costs the average number of antenatal-HIV appointments attended in this study was 3.2 per woman. This study also does not include the cost of medications prescribed to HIV patients other than HAART and prophylactic antibiotics, as these are dispensed outside the hospital setting. The total cost of vaccines (influenza, pneumococcal, hepatitis A, hepatitis B, and combined hepatitis A and B) and tuberculin dispensed to the HIV clinic was available, however as these costs could not be assigned at a patient level. The total estimated cost of vaccines and tuberculin in 2012 was €3,734 (including consumables) and even though this is probably an underestimate as patients may be vaccinated in other healthcare settings, overall it is likely to account for a relatively small proportion of the total costs of ambulatory HIV care in this centre.

4.6 Conclusion

Accurate cost data are essential for ensuring HIV services are effective, efficient, and equitable and cost information should be used to guide policy, planning and implementation [251]. This is particularly pertinent in the current situation in Ireland, as healthcare funding is undergoing restructuring. We have found that HIV outpatient costs were substantially underestimated by routine hospital cost data, and we feel that this information will be vital for the development of realistic setting of HIV outpatient appointment prices in the new funding system. In addition, as demands on the service increase due to greater numbers of patients and more complex care these cost data will be available for cost-effectiveness evaluations of new drugs, technologies and models of care.

5 Utilisation patterns and cost of hospital care for people living with HIV in Ireland in 2012: A single centre study

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A paper based on this chapter has been accepted by the International Journal of STD and AIDS (see Appendix 1)

5.1 Abstract

Data on the pattern and cost of health service use by HIV patients are required for evaluations of the cost-effectiveness of new drugs and technologies as well as being essential for service planning. The aim of this study was to identify the utilisation patterns and cost of hospital care for HIV patients in a single centre in Ireland in 2012. Data on the frequency and non-drug costs of all hospital resources used by HIV patients were extracted from a hospital activity based costing system. Cost data were analysed using a generalised linear model. A total of 328 patients, 3,672 patient months, were included in this study. Patients had a mean of 4.4 scheduled infectious disease outpatient appointments per patient year. 33% of patients also used another outpatient service, 10% in-patient services, 4% day-case service, and 14% emergency department services in 2012. Patients with very advanced HIV disease continue to incur a disproportionate amount of the total cost of providing care. This study provides baseline utilisation and cost data for use of both infectious-disease and non-infectious disease hospital services, and will be useful for service planning in light of the likely increases in resource demands.

5.2 Introduction

The epidemiology of HIV infection has changed with the availability of highly-active antiretroviral therapy (HAART). Mortality rates in those who initiate treatment early and who are highly adherent approach that of the general population [208], making HIV infection not only a chronic disease, but one with a relatively long duration and a high per-capita cost compared to other chronic diseases [9,136,244,274].

It has also become apparent that long-term infection with HIV and/or long-term ART is resulting in increasing levels of non-AIDS morbidity [245], and the prevalence of many non-infectious chronic diseases is higher in people living with HIV than in the general population [275,276].

Historically, healthcare systems have been designed to provide acute, episodic care and so tend to be less equipped to deal with chronic conditions [277]. The care needs of patients with multiple chronic conditions is particularly complex as these patients tend to have high healthcare utilisation and polypharmacy rates requiring co-ordination across multiple specialties both within and across healthcare providers. While there is currently little consensus in the literature on how to improve care integration, it is clear that in order to provide a service that improves patients outcomes and satisfaction, it is essential that the needs and characteristics of the patient population are taken into account when designing services and information management systems [278,279].

While many studies have published utilisation and/or cost data on all healthcare resources used by HIV patients, fewer studies have reported results broken down by whether the care was HIV related or not. In one study that did, the overall

admission rates of HIV patients for non-HIV related conditions were twice that of HIV-related admissions, with HIV-related admissions being more frequent than non-HIV admissions only in patients with a CD4 count < 75 cells/µl [280].

Increasing demands on HIV services have stimulated interest in the identification of more efficient means of providing those services. In developed countries, research has mainly focussed on methods of decreasing drug costs through such methods as the use of centralised procurement [162], generic drugs [127,159,160], and single tablet regimens [158,161], but reducing the frequency of visits and/or laboratory monitoring of stable, suppressed, patients have also been suggested as means of increasing efficiency without affecting patient outcomes [77,119,281,282].

In the era of widespread HAART use a large proportion of patients in care in developed countries are suppressed and may be suitable for reductions in the frequency of visits and/or laboratory monitoring [62,283]. In Ireland at least 68% of all patients in care (87% of patients on treatment) in 2009/2010 had a viral load <50 copies/ml [85]. Although stable patients are a group of particular interest, little has been published on either their use of HIV outpatient services or their use of wider health services. As postulated efficiency measures may target this group of patients in particular, data on the proportion of patients who fall into this category and their current level of health service usage would provide information on the potential savings that could be made if suggested efficiency measures were implemented.

We have previously reported utilisation rates and cost of the ambulatory HIV care service [284]. The cost of outpatient care reported in that study (based on micro-costing methodology) was estimated to be between €927-€1,019 per patient

month, 90% of which was due to the cost of HAART. On multivariate analysis, care for males and older people (≥50 years of age) was found to be significantly less expensive. This variation was mostly explained by variations in HAART regimens across groups, although older patients were also found to have significantly fewer appointments [284]. However that study focussed only on patients' use of HIV clinics and did not evaluate their use of inpatient care, emergency medicine or other outpatient clinics. The aim of this study was to identify HIV and non-HIV related hospital utilisation patterns and cost by HIV patients attending a single regional centre in Ireland in 2012.

5.3 Methods

5.3.1 Setting

We carried out a descriptive study of direct and indirect non-drug healthcare costs in CUH in 2012. CUH is a tertiary referral centre, and was one of only six adult HIV specialist centres which provided HIV care in Ireland in 2012 (the other centres are located in Dublin, Galway and Limerick). HIV care is provided solely by hospital-based practitioners, primary care physicians do not provide specialist HIV care. HIV care provided in the public system is free for Irish residents; however patients may choose to attend a consultant privately, in which case they pay a consultancy fee for their visit. The catchment area for the HIV service in CUH covers most of the southern region of Ireland (counties Cork, Kerry, Waterford and south Tipperary, a population of approximately 860,000 people). While the total number of people living with HIV in this region is unknown, as the catchment area is mainly rural it is likely that the prevalence of HIV in the region is lower than the 0.1%-0.2% estimated nationally by UNAIDS [23]. It is likely that most patients resident in the

region access HIV care in CUH as the nearest alternative HIV centre is located in Limerick (approximately 100km away).

5.3.2 Patient population

All HIV positive patients who attended the HIV centre in CUH in 2012 were identified from a pre-existing clinical patient database. Patients who attended the public HIV clinic located in CUH, or who were admitted to CUH in 2012 were eligible to be included in this study. Patients who attended any private HIV outpatient care in 2012 (full or partial year) were excluded. Patients who attended another HIV centre for their routine care (i.e. visitors to the area who attended CUH on a temporary basis) were also excluded. Patients were considered to be in-care from 01/01/2012, or the date of their first visit if they were a new patient, until 31/12/2012. Local clinical guidelines recommended monitoring of HIV patients every 3-4 months (although a small number of stable patients are monitored on a 6-monthly basis). The files of patients who did not attend any HIV clinic appointments in the last 6 months of 2012 were manually checked, and these patients were censored at the date of their last scheduled visit where appropriate.

5.3.3 Data

Information on admissions (inpatient and day-case, both public and private), outpatient appointments and emergency department (ED) visits in 2012 by the included patients was extracted from the hospital finance system (in 2012 euros) which covers both CUH and Cork University Maternity Hospital (CUMH). This system is an activity based costing (ABC) system ("Power Performance Manager") which uses top-down methodology to generate patient level hospital costs based on hospital accounting and activity data. The cost estimates include both pay and

non-pay (e.g. drugs, consumables, utilities, capital expenditure etc) costs, based on best accounting practice and in compliance with statutory requirements and Health Service Executive policies and procedures. In 2012 the finance system did not assign drug costs at an individual patient level, so this analysis was limited to non-drugs costs. Data on the cost of appointments with allied health professionals (social workers, dieticians, physiotherapists) were not included in the finance data due to concerns about the completeness of these data. Outpatient visits recorded on this system included "missed visits" (scheduled appointments which the patient did not attend without cancelling/rescheduling in advance of the clinic) but did not include cancelled appointments. While in general patients' appointments are scheduled in advance, a small number of patients may "walk-in" to a clinic without an appointment, these visits are recorded on the hospital administration system and were indistinguishable from pre-scheduled appointments in the data extracted.

Healthcare contacts for obstetric care were excluded from analysis, as maternity care is considered a normal physiological process and not an illness (attendances for joint HIV-antenatal care were not excluded). Obstetric care contacts were identified as follows:

- Admissions (inpatient or day case) with a primary diagnosis coded O00-O99 (childbirth, childbirth and puerperium)
- ED attendances at the CUMH emergency room
- Outpatient visits at the following CUMH clinics: obstetrics, ultrasound, fetal assessment, antenatal and post natal.

Utilisation data from a previous micro-costing study (Chapter 4) [284] was used to cross-check utilisation data and to provide information on whether an outpatient visit was attended or missed, as well as to provide information on the diagnostic tests linked with each outpatient ID appointment. Data on diagnoses associated with all inpatient episodes were obtained from the HIPE department of CUH. In-patient diagnoses are coded using the International Classification of Diseases 10th revision Australian Modification [285]. Up to 30 diagnoses codes can be recorded for each admission. Diagnoses codes for each in-patient episode were reviewed independently by two infectious-disease consultants (AJ and CB), and categorised subjectively as "HIV-related", "HIV-associated" or "unrelated to HIV". HIV-related diagnoses were diagnoses that were known to be related to HIV infection (e.g. candidal oesophagitis, adverse reactions to antiviral medication, Kaposi sarcoma), HIV-associated diagnoses were diagnoses for conditions associated with HIV infection (e.g. anal carcinoma), or diagnoses which were possibly related to the underlying HIV infection but which couldn't be definitely attributed to HIV infection (e.g. unspecified acute lower respiratory tract infection in a virally suppressed patient with a high CD4 count). Episodes where categorisations differed or were not possible to determine on the basis of diagnoses codes alone were re-checked by the consultant in CUH (AJ) in conjunction with a Clinical Nurse Specialist and patient notes. Admissions which occurred within 1 day of an ED visit were assumed to be linked to that ED visit. In-patient episodes admitted and discharged on the same day were given a length of stay of 1 day. The CD4 counts reported are the minimum CD4 counts recorded in 2012. A list of the variables included in this analysis and their source is shown in Table 5-1.

Table 5-1. List of variables included in analysis and source of data

Variable	Source of variable	Notes
Patient level		
Age	ABC/Micro-costing	
Gender	ABC/Micro-costing	
Risk factor	Micro-costing	
Minimum CD4 count in 2012	Micro-costing	
Late diagnosis	Micro-costing	
Years since diagnosis	Micro-costing	
Treatment status	Micro-costing	
Suppression status	Micro-costing	
Healthcare contact level		
Date	ABC	Date of healthcare contact/admission
Type of contact	ABC	Inpatient/day case/emergency dept/outpatient
Hospital	ABC	CUH/CUMH
Clinic name	ABC	
Cost	ABC	Total cost, excluding drug costs
Date of discharge	ABC	Inpatient admissions only
Length of stay	ABC	Inpatient admissions only
Number of ICU days	ABC	Inpatient admissions only
Diagnosis	HIPE	Inpatient admissions only, up to 30 recorded per admission
Procedure	HIPE	Inpatient admissions only, up to 30 recorded per admission
Attended	Micro-costing study	Outpatient appointments only
CD4 count	Micro-costing study	ID outpatient appointments only
FBC	Micro-costing study	ID outpatient appointments only
Viral Load	Micro-costing study	ID outpatient appointments only
Biochemistry profile	Micro-costing study	ID outpatient appointments only

ABC, activity based costing system; HIPE, Hospital inpatient enquiry; FBC, Full blood count

5.3.4 Ethical considerations

Ethical approval for this study was obtained from the Research Ethics Committee of

CUH.

5.3.5 Data analysis

5.3.5.1 Patient categorisation

There is no definition of what constitutes a “stable” patient, however patients who

are newly diagnosed, require antenatal care, are on HAART but not suppressed, are

not on HAART or have CD4 counts <350 cells/µl are all groups of patients who would not be suitable for less frequent monitoring [3,40,41,75]. Therefore in this analysis patients were categorised as "stable" if they met all of the following conditions:

- They were on HAART and categorised as suppressed for their entire study period in 2012 ("suppressed" defined as all viral loads in 2012 <50 copies/ml, with one test result of 50-499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml)
- They were diagnosed before the start of 2011
- Their lowest CD4 count recorded in 2012 was ≥ 350 cells/µl
- They did not attend for antenatal care in 2012

5.3.5.2 Statistical analyses

All information was entered into a Microsoft Access® database and analysed using Microsoft Excel® and STATA 12 (College Station, Texas). Mean numbers of appointments per year were calculated weighted by the number of months in care. Differences in proportions were tested using χ^2 tests, as patients had different length of follow-up during which an episode of care could happen χ^2 tests for differences in proportions were limited to the sub-group of patients who were in care for 12 months (n=287) where applicable. Differences in means of normally distributed variables were tested using the Student's t-test. Differences in non-normally distributed variables (e.g. mean costs per patient month) were tested using either Wilcoxan rank-sum or Kruskal-Wallis rank tests. A binomial generalised linear model was used to test the association between HAART status and missed

infectious disease outpatient visits, taking into account length of follow-up and patient clustering.

For comparison of stable and non stable patients, the average number (and 95% CIs) of visits and tests per patient were estimated using Poisson regression with robust standard errors. Relative risks for use of services were calculated using a modified Poisson approach with robust error variances [286].

Multivariate analysis of cost data was performed using a generalised linear model (inverse Gaussian family, identity link). The family was selected using a modified Parks test, while the link was identified by evaluating the results of the Pearson, Pregibon and modified Hosmer and Lemeshow tests for power links between 0 and 1 in increments of 0.1 [264].

5.4 Results

5.4.1 Description of cohort

A total of 328 patients (3,672 patient-months) were included in the study. The characteristics of the patient cohort has been reported previously [284]. The majority of patients (59%) were male and the average age was 40 years. 13% (n=42) were ≥50 years of age. Most patients had a minimum CD4 count in 2012 >350 cells (77%), and were on HAART for 100% of their study period (79%), a further 14% were on HAART for <100% of their study period, most of whom were patients who initiated HAART in 2012. A small proportion of patients were co-infected with hepatitis C (7%), hepatitis B (2%) or with both hepatitis B and C (1%). Three patients died, two of these were newly diagnosed in 2012 and died of HIV-related causes.

In total 61 patients were excluded. Limited data were available on the age and sex of excluded patients. Excluded patients were significantly older (mean 47 years vs 40 years, t-test p<0.0001) and more likely to be male (77% vs 59%, χ^2 p=0.005).

5.4.1.1 Stable vs non-stable patients

Of the 328 patients included in this study, 166 (51%) were classified as stable and 162 (49%) as non-stable. The characteristics of the two groups are shown in Table 5-2. Stable patients tended to be older (mean age 43 years vs 37 years, t-test p < 0.0001), and diagnosed longer (9.1 years vs 5.5 years, Mann-Whitney p <0.0001). Stable patients also contributed significantly more patient months (mean 11.6 vs 10.8 months per patient, Mann-Whitney p <0.0001).

Table 5-2. Patient characteristics of stable and non-stable patients

		Stable (%)	Non-stable (%)	Total	Chi^2, P
Total patient months		1,929	1,743	3,672	
Gender	Male	101 (61%)	93 (57%)	194	0.527
	Female	65 (39%)	69 (43%)	134	
Age group	<50 years	134 (81%)	152 (94%)	286	<0.001
	≥50 years	32 (19%)	10 (6%)	42	
Years since diagnosis	>10 years	68 (41%)	28 (17%)	96	<0.001
	6-10 years	62 (37%)	45 (28%)	107	
	1-5 years	36 (22%)	64 (40%)	100	
	Diagnosed in 2012	-	18 (11%)	18	
Risk factor	MSM	48 (29%)	48 (30%)	96	0.829
	COHP	66 (40%)	67 (41%)	133	
	Heterosexual	36 (22%)	28 (17%)	64	
	IDU	9 (5%)	9 (6%)	18	
	Other/unknown	7 (4%)	10 (6%)	17	
Late diagnosis	No	65 (39%)	72 (44%)	137	0.237
	Unknown	36 (22%)	41 (25%)	77	
	Yes	65 (39%)	49 (30%)	114	

5.4.2 Use of outpatient ID services

Infectious disease. There were 1,338 infectious-disease outpatient appointments scheduled in the 3,672 patient months in 2012 giving an average of 4.4 scheduled visits per patient year (median 4, interquartile range 3-5). While some of these appointments may have been for infectious diseases other than HIV the opinion of the clinicians providing the clinic was that the vast majority of appointments were likely to have been HIV-related. It is also worth noting that in CUH the hepatology service provides care and treatment for hepatitis C infection, and co-infected patients attend both services separately.

Missed visits. The overall missed visit rate for scheduled infectious disease clinic appointments was 12% (158/1,338), however missed visits were concentrated in a minority of patients, as 75% of patients missed no visits, 15% missed a single visit and 10% missed two or more visits. Patients not on HAART at the time of the scheduled visit were significantly more likely (odds ratio 2.7, 95% CI 1.3-5.6) to miss their appointment.

Overall stable patients had fewer visits in 2012 (average 3.30 scheduled visits per patient, 95% CI 3.13-3.36) than non-stable patients (4.95 scheduled visits per patient, 95% CI 4.57-5.33). Stable patients also attended significantly more of their scheduled visits 90% attended vs 86% attended (χ^2 p=0.025). Stable patients attended an average of 2.98 visits in 2012 (95% CI 2.86-3.10 visits per patient) while non-stable patients attended 4.28 visits in 2012 (95% CI 3.95-4.61 visits per patient).

Of the patients who were considered to be in care for the entire of 2012 (n=287), 15% attended twice, 59% attended 3 times, 18% attended 4 times and 8% attended 5 or more visits in 2012 (Figure 5-1).

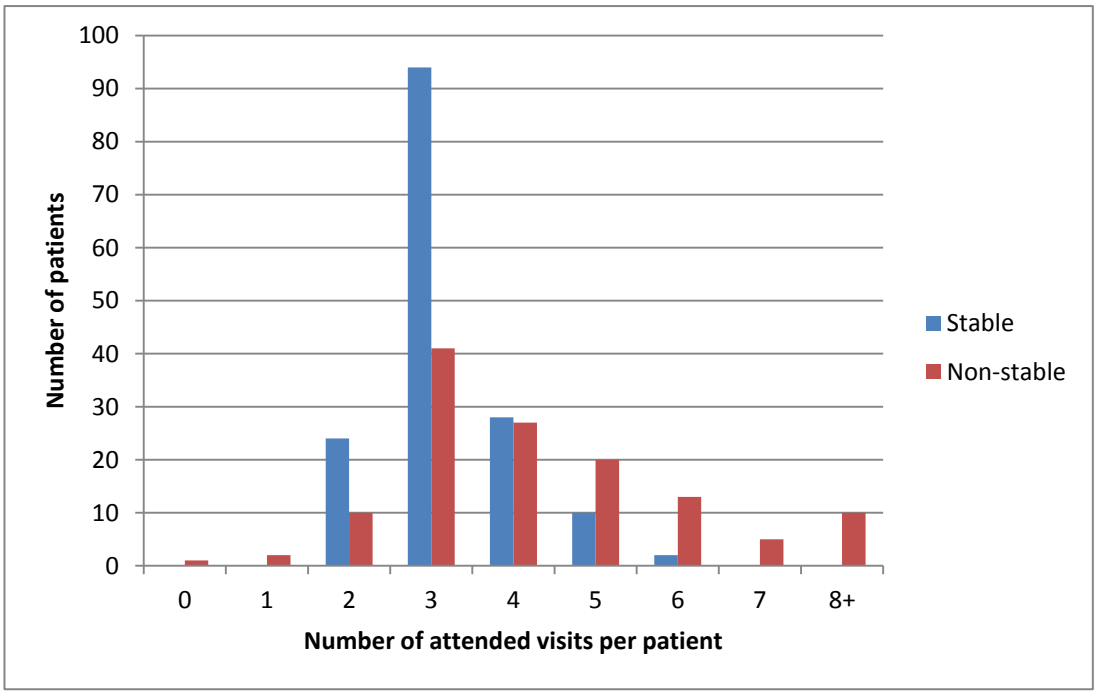


Figure 5-1. Number of attended HIV outpatient appointments per patient in 2012 in patients in care for all of 2012, by patient type (n=287)

Routine laboratory testing

There were 1,180 attended outpatient appointments in 2012, and 91% of these had at least one associated laboratory test. Local clinical guidelines in 2012 (Appendix 3) recommended patients receive CD4, viral load, FBC and biochemistry profile testing every 3-4 months.

The average number of these routinely recommended tests that patients received in 2012 is shown in Table 5-3. The distribution of the number of tests per patient (for patients in care for all of 2012) by patient type can be seen in Appendix 4.

Table 5-3. Total number of tests and mean number of tests per patient (n=328) by patient type, in 2012

	Stable patients		Non-Stable patients	
Test name	**Total number**	**Average per patient (95% CI)**	**Total number**	**Average per patient (95%CI)**
CD4	466	2.71 (2.61-2.81)	548	3.56 (3.33-3.78)
Viral Load	469	2.73 (2.63-2.83)	527	3.42 (3.19-3.65)
FBC	473	2.75 (2.65-2.85)	564	3.66 (3.41-3.91)
Biochemistry profile	483	2.81 (2.69-2.93)	560	3.63 (3.38-3.88)

5.4.3 Use of other hospital services

The overall proportions of patients with any non-ID outpatient appointment, any emergency department (ED) attendance or any inpatient admission in 2012 are shown in Table 5-4.

Table 5-4. Proportion of patients with any non-ID outpatient appointment, any ED attendance or any inpatient admission (including day-cases) in 2012

		Non-ID outpatient appointment	ED attendance	Inpatient admission (HIV related/associated, HIV unrelated)
Stable	Yes	39%	17%	15% (6%, 9%)
	No	27%	11%	6% (1%, 5%)
Gender	Male	35%	13%	11% (4%, 7%)
	Female	31%	15%	10% (2%, 7%)
Age group	<50 years	34%	15%	11% (4%, 7%)
	≥50 years	29%	10%	7% (0%, 7%)
Years since diagnosis	>10 years	33%	14%	7% (1%, 6%)
	6-10 years	37%	13%	8% (2%, 7%)
	1-5 years	27%	11%	10% (3%, 7%)
	Diagnosed in 2012	22%	39%	39% (22%, 17%)
Risk factor	MSM	31%	10%	9% (3%, 6%)
	COHP	34%	17%	8% (2%, 6%)
	Heterosexual	27%	11%	13% (5%, 8%)
	IDU	56%	11%	11% (6%, 11%)
	Other/unknown	35%	29%	24% (6%, 18%)
Late diagnosis	No	36%	15%	12% (1%, 11%)
	Unknown	36%	16%	9% (4%, 6%)
	Yes	26%	11%	9% (5%, 4%)
Minimum CD4 category	500+	28%	11%	7% (1%, 6%)
	350-499	26%	11%	6% (1%, 5%)
	200-349	48%	17%	15% (4%, 12%)
	50-199	64%	14%	14% (7%, 7%)
	<50	57%	86%	86% (71%, 29%)
HAART and Viral load category	On HAART, suppressed	33%	13%	8% (1%, 7%)
	On HAART, not suppressed/undetermined	41%	5%	9% (5%, 5%)
	Started/stopped HAART	31%	24%	20% (10%, 12%)
	Not on HAART	25%	21%	17% (8%, 8%)

5.4.3.1 Other outpatient specialties

One third of patients (n=108) had at least one outpatient appointment scheduled with a specialty other than infectious diseases (272 appointments). The most frequently scheduled non-ID outpatient appointments were gynaecology (14% of appointments), psychiatry (11%), gastroenterology (11%), haematology (8%), ophthalmology (8%) and orthopaedics (8%). Although use of non-ID outpatient specialities might be expected to be more frequent in older patients, the total proportion of patients ≥50 years of age with scheduled non-ID outpatient appointments did not differ significantly from younger patients (χ^2=0.41, p=0.52). The missed visit rate for scheduled appointments with non-ID specialties was 25%.

On univariate analysis, non-stable patients, IDUs and patients in lower CD4 categories had significantly higher risks of having any scheduled non-ID outpatient appointments (see Table 5-5). Stable categorisation and IDU remained significant on multivariate analysis, adjusting for gender, age, number of years diagnosed, risk factor and late diagnosis (CD4 category was not included as stable patients by definition had a CD4 count ≥350 cells/μl).

Table 5-5. Relative risk (RR) from univariate analysis and adjusted RR from multivariate analysis of any scheduled non-ID outpatient appointment in 2012, by patient characteristic

Patient characteristics		Any non-ID outpatient appointment(s)	
		RR	RR adj
Stable patient	Yes	-	-
	No	1.55*	1.64*
Female	Male	-	-
	Female	0.88	0.71
Age (per year)		1.00	1.00
Years since diagnosis (per year)		1.01	1.03
Risk factor	MSM	-	-
	COHP	1.08	1.35
	Heterosexual	0.85	0.95
	IDU	1.94*	2.13*
	Other/unknown	1.17	0.94
Late diagnosis	No	-	-
	Unknown	1.03	0.73
	Yes	0.72	0.69
Min CD4 category	500+	-	
	350-499	0.89	
	200-349	1.70*	
	50-199	2.43**	
	<50	2.43**	
HAART and Viral load category	On HAART, suppressed	-	
	On HAART, not suppressed/undetermined	1.26	
	Started/stopped HAART	1.22	
	Not on HAART	0.86	

Model used for both univariate and multivariate analyses was a generalised linear model with Poisson family, log link and robust standard error. *P<0.05, **P≤0.001, RR relative risk. COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/µl at diagnosis or AIDS defining illness at diagnosis. “On HAART” means the patient was on HAART for the entire duration of the study, “suppressed” was defined as all viral loads in 2012 <50 copies/ml, with one test result of 50-499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml.

5.4.3.2 Admissions

There were 43 inpatient episodes (in 34 patients) in 2012, of which 28% (n=12) were categorised as HIV-related and a further 9% (n=4) as HIV-associated. The overall in-patient admission rate was 0.14 admissions per patient year, with the average length of stay 7.5 days per admission. Eight inpatient days (2%) were intensive care days (2 patients). The primary diagnosis coded for each inpatient episode can be seen in Table 5-6. Of note was that 8 admissions (19%, 95% CI 8%-33%) did not have a HIV related diagnosis code (B20-24) recorded in any of the 30 available diagnoses fields. Nearly all of these admissions were classed as unrelated to HIV, however one was classed as HIV-associated.

Table 5-6. Number (days) of inpatient episodes by primary diagnosis code and HIV category

Primary diagnosis (ICD-10 AM chapter)	Codes	HIV-related	HIV-associated	Unrelated to HIV
Infectious and parasitic diseases	A00–B99	7 (88)		
of which, HIV diagnoses	*B20-24*	*4 (35)*		
Neoplasms	C00–D48	1 (33)		
Diseases of the blood and blood-forming organs and immune mechanism	D50–D89			1 (1)
Endocrine, nutritional and metabolic diseases	E00–E90			1 (1)
Mental and behavioural disorders	F00–F99			1 (1)
Diseases of eye and adnexa	H00–H59	1 (3)		
Circulatory system diseases	I00–I99			3 (6)
Respiratory diseases	J00–J99		1 (3)	1 (1)
Digestive diseases	K00–K93			3 (18)
Diseases of the skin and subcutaneous tissue	L00–L99	2 (5)		1 (1)
Diseases of the musculoskeletal system and connective tissue	M00–M99	1 (11)		2 (2)
Genitourinary system diseases	N00–N99		1 (1)	5 (13)
Symptoms, signs not elsewhere classified	R00–R99		2 (7)	4 (20)
Injury, poisoning and certain other consequences of external causes	S00–T98			5 (110)
Total		**12 (140)**	**4 (11)**	**27 (174)**

There were also 197 day-case admissions (defined as planned admissions not requiring an overnight stay [285]) in 2012. The vast majority of these were incurred by two patients, one on haemodialysis (158 day-case admissions) and the second undergoing radiotherapy for a HIV-associated condition (27 day-case admissions). Of the remaining 12 day-case admissions, 4 were considered HIV-related and 2 HIV-associated.

Not being categorised as stable was significantly associated with risk of any inpatient admission and any HIV-related/associated inpatient admission (but not HIV-unrelated admission) on multivariate analysis, with non-stable patients being more than twice as likely as stable patients to be admitted and over 5 times more likely to have a HIV-related/associated admission (Table 5-7). Having a risk factor of "other/unknown" was also significantly associated with an increased risk of any admission. This risk group is comprised of mixture of patients including those with an unknown risk factor as well as those who acquired HIV through exposure to blood/blood products, and vertical transmission. The elevated risk of admission in this group may possibly be explained by the likelihood of co-morbidities in these patients, particularly the patients who acquired HIV through exposure to blood products.

5.4.3.3 Emergency department visits

There were 65 ED visits by 46 patients (14% of patients), giving an average ED visit rate of 0.2 visits per patient year. 51% of these visits resulted in admission, one third of which were considered HIV-related admissions.

Having a very low CD4 count and having started/stopped treatment were significantly associated with an ED attendance on univariate analysis, however on multivariate analysis only having a risk factor of other/unknown remained significant (Table 5-8).

Table 5-7. Relative risk (RR) from univariate analysis and adjusted RR from multivariate analysis, of any admission (including day-case admissions), HIV-related/associated admissions, and HIV unrelated admissions in 2012, by patient characteristics

Patient characteristics		Any inpatient admission		HIV-related/associated admission		HIV unrelated admission	
		RR	RR adj	RR	RR adj	RR	RR adj
Stable	Yes	-	-	-	-	-	-
	No	2.66*	2.23*	11.07*	5.04*	1.84	1.81
Female	Male	-	-	-	-	-	-
	Female	0.89	0.86	0.54	0.35	1.02	1.06
Age (per year)		0.98	0.99	0.96	0.98	0.98	1.00
Years since diagnosis (per year)		0.94	0.96	0.72	0.80	1.00	1.00
Risk factor	MSM	-	-	-	-	-	-
	COHP	0.88	0.89	0.72	1.16	0.96	0.87
	Heterosexual	1.33	1.48	1.49	3.10	1.25	1.11
	IDU	1.30	1.56	1.94	2.91	1.94	1.90
	Other/unknown	2.60	3.81*	1.94	3.63	2.92	2.96
Late diagnosis	No	-	-	-	-	-	-
	Unknown	0.76	0.79	2.76	4.60	0.61	0.60
	Yes	0.71	0.83	3.62	4.16	0.32*	0.36
Minimum CD4 category	500+	-		-		-	
	350-499	0.81		0.97		0.78	
	200-349	2.17		3.26		1.96	
	50-199	2.16		6.49		1.30	
	<50	14.58**		72.88**		5.83*	
HAART and Viral load category	On HAART, suppressed	-		-		-	
	On HAART, not suppressed/ undetermined	1.20		4.81		0.69	
	Started/stopped HAART	3.51*		14.03*		2.40	
	Not on HAART	2.47		9.88*		1.41	

Model used for both univariate and multivariate analyses was a generalised linear model with Poisson family, log link and robust standard error. *P<0.05, **P≤0.001, RR relative risk. COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/µl at diagnosis or AIDS defining illness at diagnosis. "On HAART" means the patient was on HAART for the entire duration of the study, "suppressed" was defined as all viral loads in 2012 <50 copies/ml, with one test result of 50-499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml.

Table 5-8. Relative risk (RR) from univariate analysis and adjusted RR from multivariate analysis, of any ED attendance in 2012, by patient characteristics

Patient characteristics		Any ED attendance	
		RR	RR adj
Stable	Yes	-	-
	No	1.57	1.33
Female	Male	-	-
	Female	1.10	0.84
Age (per year)		0.99	1.00
Years since diagnosis (per year)		0.97	0.96
Risk factor	MSM	-	-
	COHP	1.58	1.66
	Heterosexual	1.05	1.12
	IDU	1.17	1.19
	Other/unknown	2.92*	3.87*
Late diagnosis	No	-	-
	Unknown	1.05	1.15
	Yes	0.75	0.76
Minimum CD4 category	500+	-	
	350-499	0.92	
	200-349	1.54	
	50-199	1.37	
	<50	9.21**	
HAART and Viral load category	On HAART, suppressed	-	
	On HAART, not suppressed/undetermined	0.36	
	Started/stopped HAART	2.49*	
	Not on HAART	1.83	

Model used for both univariate and multivariate analyses was a generalised linear model with Poisson family, log link and robust standard error. *P<0.05, **P≤0.001, RR relative risk. COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/µl at diagnosis or AIDS defining illness at diagnosis. “On HAART” means the patient was on HAART for the entire duration of the study, “suppressed” was defined as all viral loads in 2012 <50 copies/ml, with one test result of 50-499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml.

5.4.4 Costs

The non-drug cost to the hospital of providing care for the HIV patients included in this study in 2012 can be seen in Table 5-9.

As would be expected, the type of costs incurred differed by CD4 category, with patients with lower CD4 counts having a higher proportion of their costs due to HIV-related inpatient care, while those with higher CD4 counts had little HIV-related inpatient care. Most notably, the 2% of patients with a CD4 count < 50 cells/µl accounted for 61% of inpatients costs (€194,369/€317,892) and 31% (€209,725/€669,591) of the total cost of providing care for HIV patients in 2012.

The overall mean non-drug cost per patient month (PPM) was €180 (€95-€265). On univariate testing (Wilcoxan rank-sum or Kruskal-Wallis tests) the total non-drug costs per patient month differed significantly by age group ($p<0.0001$), risk factor ($p=0.04$), stable categorisation ($p<0.0001$), CD4 category ($p=0.0001$), year of diagnosis ($p<0.0001$), and HAART/suppression category ($p=0.0001$). However on multivariate analysis of total non-drug costs the only predictors that remained significant on adjustment were CD4 < 50 cells/µl and not being on HAART (Table 5-10).

Table 5-9. Proportion of non-drug costs by type of care, proportion of patients who used each care type (n=328), and for those who used each type of care the mean, median and inter-quartile range (IQR) of non-drug costs per patient month, 2012.

	% of total non-drug costs	% of patients incurring cost (95% CI*)	Non drug cost per patient month		
			Mean	Median	IQR
Outpatient appointments					
Infectious diseases	35%	100%	€ 63	€ 54	€45-€72
Other specialties	11%	33% (28%-38%)	€ 59	€ 18	€10-€32
Outpatient subtotal	*46%*	*100%*	*€ 84*	*€ 60*	*€46-€87*
Inpatient episodes					
HIV related	19%	3% (2%-6%)	€ 1,584	€ 656	€291-€1,968
HIV associated	1%	1% (0.2%-3%)	€ 207	€ 159	€146-€317
Unrelated to HIV	27%	7% (5%-11%)	€ 722	€ 138	€66-€358
Inpatient subtotal	*47%*	*10% (7%-14%)*	*€ 958*	*€ 182*	*€75-€879*
Day case admissions					
HIV related	0%	1% (0.2%-3%)	€ 55	€ 47	€18-€97
HIV associated	1%	1% (0.2%-3%)	€ 258	€ 57	€56-€661
Unrelated to HIV	3%	2% (1%-4%)	€ 251	€ 46	€16-€60
Day case subtotal	*5%*	*4% (2%-7%)*	*€ 212*	*€ 56*	*€24-€60*
Emergency Department visit					
All ED visits	2%	14% (11%-18%)	€ 27	€ 17	€14-€25
Total	**100%**		**€ 180**	**€ 61**	**€46-€93**

*Agresti-Coull 95% Confidence Interval.

Table 5-10. Mean HIV related/associated, HIV unrelated and total non-drug costs ppm 2012, by subgroups, and significance of differences in total non-drug costs on multivariate analysis.

Patient subgroup		N	Mean cost ppm			Multivariate analysis of total nondrug costs, P
			HIV related/ associated	HIV unrelated	Total	
Gender	Male	194	121	111	235	ref
	Female	134	79	24	101	0.86
≥50 years	No	286	112	84	197	ref
	Yes	42	48	18	68	0.11
Risk factor	MSM	96	151	49	203	ref
	COHP	133	78	33	112	0.46
	Heterosexual	64	73	32	104	0.11
	IDU	18	94	530	629	0.64
	Other/unknown	17	170	275	453	0.46
Minimum CD4 count in 2012	500+	169	58	22	82	ref
	350-499	85	67	58	122	0.49
	200-350	52	103	119	223	0.20
	50-199	14	176	143	323	0.06
	<50	7	1840	1340	3227	0.02
Late diagnosis	No	137	75	61	136	ref
	Unknown	77	76	173	251	0.08
	Yes	114	156	28	186	0.11
Years since diagnosis	11+ years	96	57	81	140	ref
	6-10 years	107	69	98	168	0.97
	1-5 years	100	108	20	126	0.66
	diagnosed 2012	18	918	380	1319	0.28
HAART & Viral load category	On HAART suppressed	211	64	46	111	ref
	On HAART not suppressed/undetermined	44	137	55	187	0.71
	Started/stopped HAART	49	293	293	591	0.37
	No HAART	24	98	26	128	0.03

PPM, per patient month. Total non-drug costs ppm includes the cost of ED visits. Generalised linear model with inverse Gaussian family and identity link. Ref, reference category. COHP, person from a country of high prevalence with no other identifiable risk factor available. MSM, men who has sex with men. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/µl at diagnosis or AIDS defining illness at diagnosis. "On HAART" means the patient was on HAART for the entire duration of the study, "suppressed" was defined as all viral loads in 2012 <50 copies/ml, with one test result of 50-499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml.

5.5 Discussion

This study reports the range, frequency and cost of healthcare services used by HIV patients in a single centre in the south of Ireland in a single calendar year (2012).

We have previously reported the cost of HAART for this cohort in 2012 was €856 per patient month [284], making HAART costs over 80% of the total cost of providing care in 2012 (excluding other drug costs). This is a similar proportion to what has reported previously in other countries [121,134,266,267]. Although HAART is expensive, it is a very cost-effective treatment [42,269,287], and not only vastly improves individual outcomes, but also has population level benefits, reducing onward transmission [270]. In this cohort, 77% of patients were on HAART for the entire period of the study with a further 11% initiating HAART during 2012, just 7% of patients received no HAART in 2012 (their average CD4 count was 510 cells/µl). Of patients who were on HAART for more than 6 months, the most recent viral load result was <50 copies/ml for 90% of patients, treatment and response figures which are comparable to other developed countries [248-250].

Unsurprisingly outpatient infectious disease care was the most frequently used service by this group of patients, accounting for 35% of all non-drug costs in 2012 (Table 5-9). One third of patients also had outpatient appointments with other specialties, and while the overall cost of non-ID outpatient appointments was 11% of total non-drug costs, within the subgroup of patients using other services nearly half (47%) of their outpatient costs were due to use of non-ID services. It is well established in the literature that as patients age they are experiencing increasing levels of non-HIV morbidity [237], rates of which are higher than in comparable HIV

negative populations [275,288]. It is a limitation of our study that we do not have information on patient co-morbidities, and can only use other services as an indicator of possible non-HIV morbidity. Hospital outpatient appointments are likely to underestimate the burden of non-HIV morbidity as infectious disease specialists may be dual trained or patients may attend other hospitals/primary care services for their non-HIV care. Conversely patients may also be referred to other specialties for investigations that subsequently prove negative. There were relatively few patients ≥50 years of age in this cohort in 2012 so unfortunately it was not possible to carry out any meaningful analysis of their use of specific non-ID services. In contrast to what has previously been reported in the literature [134] the cost of care for older patients in this study was lower than that for younger patients, although this was no longer significant when adjustment was made for confounding factors (Table 5-10). We previously reported a similar finding for the cost of HIV outpatient care alone, and postulated that this result was due to the particular characteristics of the cohort attending CUH [284]. However this study does provide baseline data which will be useful to assess potential changing resource use with the ageing of the patient cohort.

An interesting finding was that 19% (95% CI 8%-33%) of admissions had no HIV diagnosis coded in any of the 30 available diagnoses fields. There are two possible reasons for this discrepancy, HIV diagnoses may not have been documented in the medical records available to the coders (as doctors may not have asked about, or patients may not have disclosed their HIV status), or errors may have occurred during the coding process. Previous studies examining the accuracy of diagnostic

coding in Irish public hospitals have highlighted the limitations of such data for research purposes [289-291]. The benefits of clinician awareness of and involvement in the coding process has previously been demonstrated [290] and as healthcare funding structures in Ireland change, from block grant budgets to an activity based "money follows the patient" approach [258], clinician education on the importance of clear and complete documentation as well as regular auditing of coding and detailed analysis of local data to identify possible data quality issues [292-294] are likely to become critical factors in hospital funding.

Approximately half of the patients attending CUH in 2012 for HIV care were categorised as stable. Although 64% of patients in our study were on HAART and suppressed for the study period 16% of those patients had CD4 <350 cells/μl, and so were not categorised as stable in this analysis. Over half of these patients were known to have been diagnosed late, and baseline CD4 count is one of the most important factors determining the CD4 recovery of patients on treatment [295-300]. This illustrates one of the longer-term consequences of late diagnosis for the health service, as patients diagnosed late will on average take longer to achieve the required CD4 levels necessary for reduced monitoring.

In terms of the use of the outpatient HIV service, as would be expected stable patients were found to have significantly fewer outpatient ID appointments (both scheduled and attended), and significantly fewer routine tests per year than patients who were not categorised as stable. A small proportion of patients had more frequent attendances than would be expected for truly stable patients, indicating that perhaps these patients had additional clinical needs which were not

covered in the criteria used to categorise patients in this analysis, and perhaps would not, in reality, be suitable candidates for reduced clinical and/or laboratory monitoring. An audit carried out in CUH in 2013 reported a similar proportion (50%) of patients were suppressed with a CD4 count > 350 cells/μl, but only 52% of those patients in that study were deemed eligible to be scheduled for 6-monthly review [301].

On average, stable patients attended nearly 3 visits per year, and accounted for 44% of all attended HIV outpatient visits in 2012 (n=514), assuming the average number of visits per patient could be reduced to 2 visits per year, there would be approximately 180 fewer visits, equivalent to around a 15% reduction in the total number of attended outpatient infectious disease visits. If this reduction was only possible in 52% of the stable patients (as suggested by the audit in CUH), then there would be an equivalent reduction in total visits of less than 9%.

Laboratory monitoring is another area where it has been suggested that cost-savings could be made through the reduction in the number of tests performed. In recent years, evidence has emerged the CD4 counts of stable patients change little, leading to international guidelines reducing their recommended frequency of monitoring in stable patients on treatment , in particular in those which high CD4 counts (see Appendix 5) [3,41,302]. This cohort of patients, had an average of around 2.7-2.8 of each of the four routinely recommended tests (CD4, viral load, FBC, biochemistry profile) performed per year. Within current guidelines CD4 testing and FBCs could theoretically be performed annually, while VL and biochemistry profiles could be performed 2/year (Appendix 5). A reduction in

testing of that magnitude would result in a saving of approximately 40% of routine test costs in stable patients, and routine tests account for over 80% of the total laboratory testing costs associated with HIV outpatient visits (see Chapter 4).

On multivariate analysis non-stable patients were found to have a significantly higher risk of using any non-ID outpatient service (RR 1.64), and were also over five times as likely to have a HIV related/associated inpatient admission compared to stable patients (see Table 5-7).

We recognise that there are several important limitations to this study. The study was carried out in a single centre which has a lower proportion of injecting drug users than the total HIV population in care in Ireland (6% vs 21% nationally), however the study population was similar to the national HIV population in care in terms of age (mean age 40 years for both), gender (59% male CUH vs 62% male nationally) and clinical characteristics (80% on HAART nationally) [85]. No information was collected on patients' use of other hospitals, while the nearest alternative HIV centre is 100km away, there are four other hospitals in the region providing emergency care which patients could have accessed and which would not have been included in this study. The cost of appointments with allied health professionals within CUH was not included nor was any patient use of non-hospital health services (GPs, community care). It was also not possible to distinguish HIV-morbidity associated use of non-ID outpatient hospital services. As a clinical database routinely updated with viral load results was used to initially identify all patients who attended in 2012, eligible patients may have been missed if a patient attended and did not have a viral load test performed or if the viral load was not

entered on the database. As the possibility of a patient who had attended in 2012 but who had no corresponding viral load result in the database would be more likely to happen if a patient only attended once in 2012, this could be a source of selection bias in this study. Probably the biggest limitation, however, is the lack of a HIV negative comparison group, meaning it was not possible to estimate how much healthcare use in this cohort was additional to what would be normally used by similar patients without HIV infection. National surveys have reported the 12-month prevalence of use of hospital services by the general population to be 10% for emergency services, 20% for outpatient services, 9% for day patient admissions, and 10% for in-patient admissions [303,304]. The overall prevalence of ED and non-ID outpatient clinic use were higher in our study (14% and 33% respectively) as were the age-specific rates. The proportion of patients admitted following an ED episode (51%) was also higher than the reported proportion of ED episodes that result in admission overall in Ireland (25%) [305]. The prevalence of non-HIV admissions (7%) and day-case admissions (4%) was slightly lower than the prevalence in the general population, although this difference may be explained by the exclusion of obstetric care from our analyses.

Data on the use and cost of health service use by HIV patients is very useful for both planning of health services and for use in health technology assessments and cost-effectiveness studies. The prevalence approach to costing, as used in this study, is particularly informative for policy makers and planners as it provides a snapshot of the total cost for a particular year given the mix of patients present, whereas an incidence approach, which would be better at identifying and estimating the costs

for particular types of patients, or particularly resource intensive periods of patient care (e.g. following diagnosis, approaching death etc) does not necessarily provide the type of information that can be easily used for planning. Information on the range and frequency of other specialties accessed by this population can also be used to inform the long-term organisation of services and co-ordination and integration of care across specialties.

There is no agreed definition of what constitutes a "stable" patient, British [42], European [41] and WHO[40] guidelines give no definition of how long a patient should be suppressed to be considered "stable" while US guidelines specify 2 years [3]. We did not have data on the suppression status of patients before the start of data collection in 2012, so our categorisation may have over-estimated the proportion of patients who were stable. Data on patient co-morbidities, which would require more frequent clinical follow-up, were not available, again possibly inflating the proportion of stable patients in this analysis. In addition, laboratory tests were linked to outpatient appointments based on matching dates, the use of the data as a linking variable may have missed some laboratory results, underestimating the number of laboratory tests performed.

While our study provides baseline information on the frequency and type of hospital services used by HIV patients, further work to estimate the costs and resource use during intensive phases of care, such as following diagnosis, or approaching death would be useful for making more accurate estimates for health technology assessments and cost-effectiveness analyses. As Ireland's healthcare financing structures are reformed, it is particularly important that the costs of

complex patients, such as HIV patients, are adequately accounted for in new financing structures.

6 Cost and variation of ambulatory HIV care in Ireland

6.1 Abstract

It is anticipated that demands on ambulatory HIV services will increase in coming years due to increases in both the size and age profile of the patient population. Data on current service delivery patterns and costs are needed to allow evaluation of the estimated impact of the changing epidemiology and/or changes to international clinical guidelines, as well as to facilitate health technology assessments of new drugs and models of care. Differences in organisation of care as well as economies of scale make national extrapolation of cost data generated in a single centre problematic. The aim of this research was to generate a national estimate of the annual cost of outpatient HIV care taking into account local variation in service delivery.

Visit costs were based on results of a single centre micro-costing study. In order to account for variation in organisation of care across centres information collected through expert interviews with key staff was used to adjust the staff portion of visits costs for each centre. A decision tree was developed based on groups of patients with different visit rates (antenatal patients, new patient patients, patients who started or switched HAART regimens) and populated using data from the micro-costing study and average annual staff costs weighted by centre. Uncertainty was explored using both one-way and probabilistic sensitivity analysis.

The average base-case annual non-drug cost of care in 2012 was estimated to be €1,127 per patient (IQR on PSA €1,008-€1,230). On one-way sensitivity analysis, uncertainty associated with staff costs and diagnostic tests resulted in the greatest variation in estimated costs (±9% and ±34% respectively). The estimated annual

non-drug cost for individual centred varied by up to 20% from the base-case estimate.

The results of this research show the importance of taking variation in service delivery into account when generating cost of illness estimates at a national level.

6.2 Introduction

The micro-costing study described in Chapter 4 resulted in an estimate of the monthly cost of outpatient HIV care per patient in a single centre (CUH). As unit costs and utilisation patterns in any specific location may be related to each other as well as being affected by the complex interplay of local (e.g. disease, patient and clinician characteristics) and higher level factors (e.g. health system and socio-economic characteristics), the generalisability of cost estimates generated in a single centre can be limited [163].

The majority of the literature examining cost variability between centres has focused on the problem of cost data generalisability at an international level [163,306,307]. However, the same issues exist between centres within countries [163]. Information on the variability of outpatient costs within countries is particularly limited. Data from a European project (HealthBASKET) examining the variation of costs for 10 healthcare services (both inpatient and outpatient), both within and between countries using case-vignettes, found that the within-country correlation of costs (as measured by the intra-cluster correlation coefficient, ICC) varied between 0.43 and 0.94 for outpatient care [308]. While a study of outpatient first-visits for oral-contraceptives found the cost of what was considered a very standard type of outpatient visit ranged from $42-$206 (mean $90) between sites in the United States [309].

That the unit costs of outpatient visits vary between centres within individual countries is not surprising, given that outpatient visits may occur in a variety of settings (tertiary referral centre, district hospital etc) and each visit consists of a

number of different steps performed by a variety of staff. Variation can occur in the individual steps that make up an outpatient visit, the type of staff involved in each step, as well as the diagnostic tests ordered and medications.

In the case of ambulatory HIV care in Ireland, while all care is provided by the ID Departments of tertiary hospitals following international best practice guidelines [3,41,42], local variation in the organisation of HIV services is likely to affect the per patient cost of providing ambulatory HIV care in each centre. When estimating average costs as a national level how costs are dealt across centres can affect the average cost estimates generated and variation in costs between centres should be taken into account where possible [310].

The aim of this chapter was to generate a national estimate of the annual cost of outpatient HIV care taking into account local variation in service delivery.

6.3 Methods

6.3.1 Ethical considerations

Ethical approval to collect data on the organisation and characteristics of the adult HIV outpatient centres using expert interviews was obtained (Appendix 6) from the research ethics committees of: Beaumont Hospital, MMUH, SJH, UCHG, and UHL.

6.3.2 National data collection

Data was gathered using surveys and face-to-face group interviews with key staff at each centre. Any issues requiring clarification were followed up by email/telephone.

6.3.2.1 Survey

A short survey was designed to collect data on the number and type of staff involved in providing HIV care, and the characteristics of out-patient clinics (Appendix 7). This survey was emailed to the consultant at each participating centres prior to the face-to-face interview. The participants had the option of completing and returning the survey prior to the meeting or at the time of the interview.

6.3.2.2 Expert interviews

Contact was made with each centre and a meeting arranged with the consultant and key members of HIV team (as nominated by the consultant). The interviews were semi-structured as the primary aim was to elicit information on how the services were organised in 2012.

The interviews were loosely structured as follows:

1) A brief introduction was given to the staff on the background to the study.

2) Discussion on the patient population and the services provided and numbers of staff in 2012 (e.g. the total patient population, the number, types and frequency of clinics, the approximate number of patients attending each clinic, the number of whole time equivalent (WTE) staff members working on outpatient HIV care, non patient-facing time etc). In cases where the number of staff differed in 2012 from the usual staffing levels (e.g. due to staff not being replaced while on maternity leave) the usual staff staffing level was used.

3) Discussion on the individual visit steps in 2012 for each type of clinic identified. To aid this process, visit flow-charts were developed prior to the meetings, based on the steps of an outpatient visits in CUH (Appendix 8), were presented and similarities/differences noted and discussed.

4) Discussion on breakdown of patient populations, based on patient groups with significantly different outpatient visit rates as identified in the micro-costing study (new patients, antenatal patients, patients starting/switching HAART).

Following each site visit, centre-specific visit flow-charts were developed based on the expert opinion based information gathered during the interviews and fed back to the key staff in each centre for approval.

The centre specific flow-charts, (along with information on non patient-facing times where available) were used to generate centre-specific estimates of unit costs of typical HIV outpatient visits in 2012. Where participants were not able to provide a local estimate, estimates were taken from the micro-costing study in CUH. It was not possible to collect specific details of staff and visits in clinics held off-site (e.g. in prisons, drug-treatment clinics and antenatal hospitals) as ethical approval was not sought for these other sites which were identified during the data collection process.

6.3.3 Cost model

Decision modelling is a widely used method in economic evaluations. Decision models provide a structured framework for decision making, and have the benefits of being able to incorporate data from a wide range of sources, as well as

facilitating the assessment of uncertainty through either probabilistic or deterministic sensitivity analysis [252].

A simple decision tree was developed using Microsoft Excel® (Figure 6-1). The branches of the tree represented groups of patients with differing utilisation rates as identified in the micro-costing study (Table 6-1). Each branch was then associated with an annual cost, generated by combining average annual visit cost for each group of patients (i.e. the centre specific unit cost per visit multiplied by the average number of visits per arm) and the average annual cost of diagnostic testing for the same groups of patients. The decision tree was then used to calculate the overall average annual cost per patient.

The same perspective and cost year were used for the cost model as were previously used in the micro-costing study: the healthcare provider in 2012.

Table 6-1. Mean number of ID outpatient visits per month, by patient group (with Poisson 95% CI)

Patient group		**Mean number of ID outpatient visits per month**
New patient	No	0.30 (0.29-0.32)
	Yes	0.59 (0.47-0.72)
Antenatal care	No	0.31 (0.29-0.33)
	Yes	0.52 (0.41-0.64)
Started/switched HAART	No	0.28 (0.26-0.30)
	Yes	0.45 (0.41-0.50)

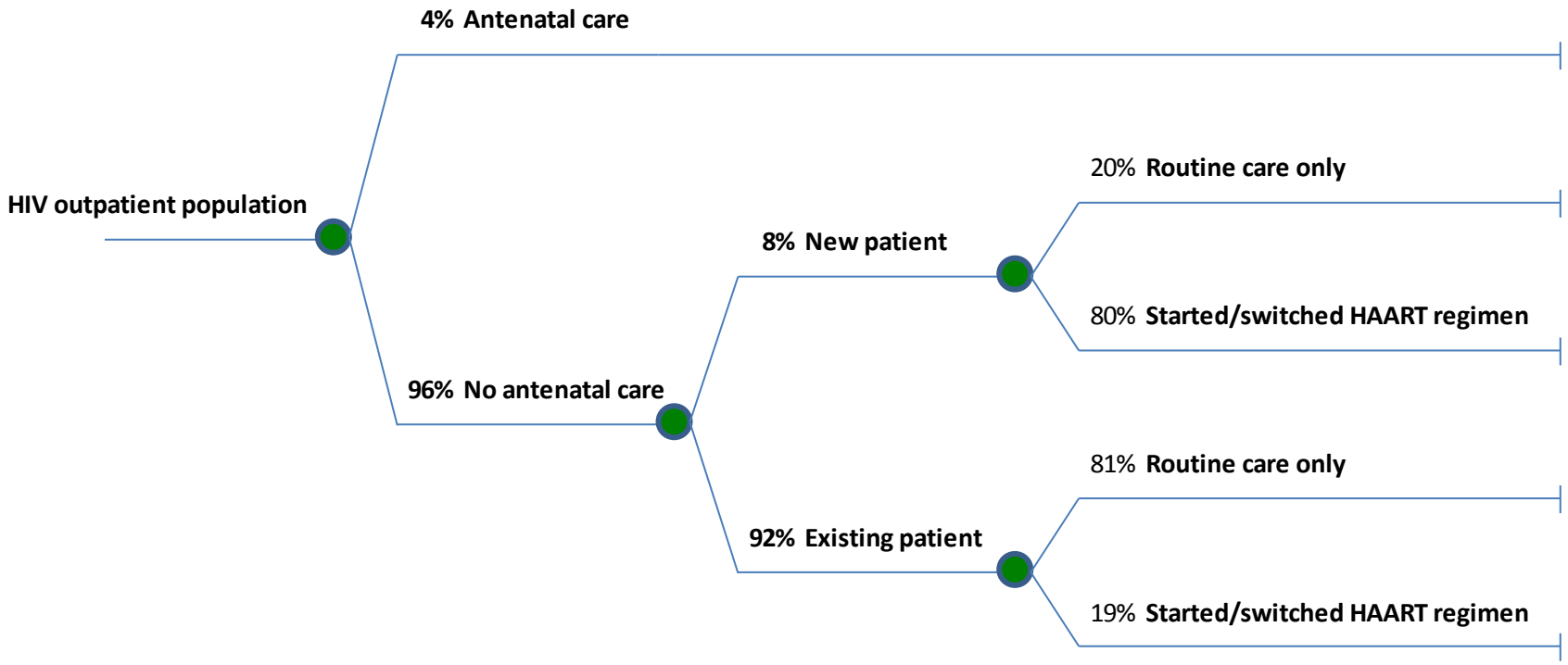


Figure 6-1. Structure of cost model

6.3.3.1 Base case estimates

Annual patient costs were separated into staff costs (patient-facing and non patient-facing time) and diagnostic testing costs. The base case staff costs, weighted by centre were estimated for each branch of the model as follows, using Microsoft Excel® and STATA 12 (College Station, Texas):

1) The estimated staff costs of each visit types in each centre was associated with the utilisation data from the micro-costing study i.e. generating a hypothetical staff cost for each centre, given the same resource utilisation as in CUH.

2) The annual mean staff cost (and standard deviation) of each branch for each centre was then calculated using a generalised linear model (inverse Gaussian family, identity link). The choice of family and link used in the model were assessed using a modified Parks test [264]).

3) A weighted mean annual staff cost for each branch was then calculated based on the proportions of patients attending each centre (as reported in a prevalence study carried out in 2009/2010 [85]). In order to account for uncertainty in the staff costs as well as in the proportions of patients attending each centre a probabilistic model (with 10,000 iterations) was used to generate a weighted mean and variance. Proportions of patients attending each centre were assumed to follow a Beta distribution while costs were assumed to follow a Gamma distribution [311].

4) The average staff cost and variance for each branch generated by this probabilistic model was used as the base case estimate of annual staff costs per branch.

The base case cost of diagnostic testing was based solely on the mean annual per patient cost of diagnostic testing estimated in the micro-costing study.

6.3.3.2 Sensitivity analysis

Both probabilistic sensitivity analysis (PSA) as well as deterministic one-way sensitivity analysis were used to examine uncertainty in the model. Sensitivity analyses were performed using Microsoft Excel®.

PSA was used to assess uncertainty in the base case estimate of annual patient cost. The list of input parameters included in the PSA are shown in Table 6-2 along with the distributions used and 95% CIs/IQRs. The beta distribution was used for proportions of patients in each arm of the model and the gamma distribution was used for costs [311]. The number of iterations in the PSA was 10,000.

One way sensitivity analysis was used to assess structural uncertainty in the model. Staff costs were varied by ±20% and diagnostic testing costs were varied by ±60% based on the same rationale as reported for the one way sensitivity analysis of the micro-costing study (Chapter 4).

Proportions of patient in each arm of the model were varied based on 95% confidence intervals based on the results of the utilisation data collected as part of the micro-costing study.

An alternative estimates was also generated based on the use of the published national cost of an outpatient visit (€130 in 2011) [256].

Table 6-2. Model parameters for PSA

Parameter	%	95% CI	Distribution in PSA
Antenatal	4%	2%-7%	Beta
Non-Antenatal	96%	93%-98%	Beta
New patient (excl antenatal)	8%	5%-11%	Beta
Existing patient (excl antenatal)	92%	89%-95%	Beta
New patient, no antenatal, routine	20%	3%-37%	Beta
New patient, no antenatal, started/changed ART	80%	63%-97%	Beta
Existing patient, no antenatal, routine	81%	77%-86%	Beta
Existing patient, no antenatal, started/changed ART	19%	14%-23%	Beta
Mean annual costs			
Antenatal patients – staff	€891	€849-€931*	Gamma
Antenatal patients – diagnostic testing	€948	€744-€1,152	Gamma
New patients, no antenatal care – staff	€422	€393-€448*	Gamma
New patients, no antenatal care – diagnostic testing	€695	€414-€879	Gamma
New patient, no antenatal care, started/changed HAART - staff	€594	€573-€616*	Gamma
New patient, no antenatal care, started/changed HAART – diagnostic testing	€965	€648-€932	Gamma
Existing patient, no antenatal care - staff	€427	€421-€432*	Gamma
Existing patient, no antenatal care – diagnostic testing	€568	€532-€591	Gamma
Existing patient, no antenatal care, started/changed HAART - staff	€618	€605-€632*	Gamma
Existing patient, no antenatal care, started/changed HAART – diagnostic testing	€751	€650-€809	Gamma

Wilson/Agresti-Coull 95% CIs for proportions. Means and 95% CIs for diagnostic test costs estimated from generalised linear model with Gamma family and identity link (family/link selection assessed using modified Parks test [264]) based on micro-costing data. * IQR, based on results of probabilistic estimate of mean staff costs.

6.3.4 HAART data

Early in the data collection process, it became apparent that most of the centres would not be able extract data from pharmacy information systems on the volume of HAART regimens dispensed. As an alternative, data on the volume and total

value of HAART drugs supplied from wholesale to hospital pharmacies was obtained from a commercial data company (IMS health).

IMS health collects data on pharmaceutical sales in Ireland at the point of sale to pharmacies. They source around 16% of their data in Ireland from manufacturers and 84% from wholesalers and the data covers 99.9% of the retail and 97% of the hospital market (personal communication). Data on the total volume and sales of all HAART drugs, in Ireland from 1995 to 2014 were provided by IMS. The breakdown by drug class was available from 2007. The volume data was supplied in terms of "units" of drugs, "units" refer to the number of packs issued. As HAART drugs generally come in the form of monthly packs, units were assumed to be equivalent to a single month of an individual ARV. As a patient regimens are usually made up of a combination of two or more medications (unless on a single-tablet regimen), the number of units is not equivalent to the number of patient regimens. It should also be noted that the sales values provided by IMS health do not include any discounts negotiated between wholesalers and individual hospitals, so will over-estimate the cost to the health service. Information on discount rates is commercially sensitive information but substantial discounts may be negotiated, particularly for off-patent products [312]. In Ireland, only one generic HAART drug, nevirapine, is currently available. Nevirapine, however is not a commonly used HAART drug, only 5% of the regimen-months dispensed in CUH in 2012 contained nevirapine. The IMS data would also include HAART used by patients not attending the public clinics (i.e. private patients), the proportion of patients attending

privately for HIV care is unknown. The classification of HAART drugs used by IMS is shown in Table 6-3.

Table 6-3. Drug classification used by IMS health.

Level 1	Level 2	Brand name	Active ingredients
J05C HIV antivirals	J05C1 Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Truvada	emtricitabine / tenofovir disoproxil fumarate
		Kivexa	Abacavir / lamivudine
		Viread	Tenofovir disoproxil fumarate
		Combivir	Lamivudine / zidovudine
		Ziagen	Abacavir
		Epivir	Lamivudine
		Emtriva	Emtricitabine
		Trizivir	Abacavir (as sulfate) / lamivudine / zidovudine
		Retrovir	Zidovudine
		Videx	Didanosine
		Zerit	Stavudine
	J05C2 Protease inhibitors (PIs)	Prezista	Darunavir
		Reyataz	Atazanavir sulphate
		Norvir	Ritonavir
		Kaletra	Lopinavir / ritonavir
		Telzir	Fosamprenavir calcium
		Invirase	Saquinavir
		Aptivus	Tipranavir
		Viracept	Nelfinavir
	J05C3 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Intelence	Etravirine
		Sustiva	Efavirenz
		Viramune	Nevirapine
		Edurant	Rilpivirine hydrochloride
		Nevirapine Teva	Nevirapine
	J05C4 HIV entry inhibitors	Celsentri	Maraviroc
		Fuzeon	Enfuvirtide
	J05C5 HIV integrase inhibitors	Isentress	Raltegravir
		Tivicay	Dolutegravir
	J05C9 Other HIV antivirals (multi-class combinations, MCCs)	Atripla	Efavirenz / emtricitabine / tenofovir disoproxil fumarate
		Eviplera	Emtricitabine / rilpivirine hydrochloride /tenofovir disoproxil fumarate
		Stribild	Elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate
		Triumeq	Abacavir sulfate / dolutegravir sodium / lamivudine

6.3.5 Cost projections

The cost of providing ambulatory HIV care for the years 2013-2020, in 2012 prices, was calculated by multiplying the estimated number of patients in care each year (estimated in Chapter 2) by the total estimated annual cost of care per patient. The total estimated annual cost of care per patient was calculated by adding the annual non-drug cost per patient estimated in this chapter with the annual cost of HAART per patient in care. Two different sources of HAART cost data were used. The first was the average cost of HAART per patient in care in 2012, €9,601, as estimated in the micro-costing study in CUH (Chapter 4). The second was the average HAART sales per patient in care as estimated using IMS sales data for 2012.

Sensitivity analysis

One-way sensitivity analysis was carried out to investigate uncertainty in the estimates used. The annual non-drug cost of outpatient care per patient and the number of patients in care each year were both varied from their base cases to the minimum and maximum estimates generated by sensitivity analyses.

6.4 Results

6.4.1 Expert interviews

The expert interviews took place between 24/02/2015 and 17/06/2015. The number and type of staff interviewed is shown in Table 6-4.

Table 6-4. The number and type of staff who participated in expert interviews

Staff	UCHG	Beaumont Hospital	UHL	MMUH	SJH
Consultant	2	1	1	1	1
Specialist nursing	1	1		1	1
Pharmacy	1*	1	1*	1	1
Other				Clerical manager	Clerical manager, vaccine nurse, research nurse, data manager, social worker

* email contact only

6.4.1.1 Summary description of services

The outpatient care provided by all six adult HIV centres in Ireland is generally quite similar and follows international best-practice guidelines [3,40,42]. On diagnosis patients generally receive a comprehensive health screen including a full STI screen, and a chest x-ray, as well as counselling regarding their diagnosis. All patients are monitored regularly, generally on a 4-6 monthly basis for stable patients, but more frequently on initiating or switching of HAART regimen (until fully suppressed), or if pregnant. There are additional vaccinations recommended for people living with HIV (both on diagnosis and on an on-going basis) [313] and HIV positive women are recommended to receive an annual cervical smear [314]. Some centres provide these services to patients as part of the outpatient HIV services however other centres generally refer patients to primary care for vaccinations and/or cervical smears. ID services also provide additional day-patient services (e.g. nebulised pentamidine) as well as in-patient care as required.

Beaumont Hospital, Dublin

The HIV centre in Beaumont Hospital provides care for approximately 11% of HIV patients attending care in Ireland [85].

The patient population is made up of a relatively high proportion of non-Irish patients due to its proximity to the direct provision centre in Balseskin, but has a lower proportion of people who inject drugs than the other Dublin centres.

Ambulatory HIV care is provided during two general ID clinics per week, approximately 80% of appointments at the clinics are HIV related. Patients are seen by either a consultant or a non-consultant hospital doctor (NCHD) with consultant review. All patients are also seen by a CNS/CNM/staff nurse as part of a routine outpatient visit. A pharmacist and social worker are available on-site at the clinic. There is a team focus on medication adherence. Patients co-infected with TB/hepatitis B/hepatitis C receive treatment for their co-infection(s) in the ID clinic. HIV positive patients requiring antenatal care attend obstetric care separately.

Patients are routinely screened for STIs on diagnosis and annually (and as required) thereafter. A weekly nurse led-clinic also provides recommended vaccines (HAV, HBV, influenza and pneumococcal vaccines), annual cervical smear tests for female patients, monthly LFT monitoring of patients with latent TB and monthly nebulised pentamidine for HIV patients allergic to septrin. Patients also receive regular glucose and cholesterol screening.

University College Hospital Galway

The HIV centre in UCHG provides care for approximately 5% of patients attending for HIV care in Ireland [85].

One mixed clinic (general medicine, ID, OPAT and HIV) and one nurse-led clinic is held per week. All patients are seen by a consultant or a registrar/SHO with consultant review. Patients are also routinely seen by a clinical nurse specialist as part of their outpatient visit. There is currently no pharmacist support at the clinic itself, relevant medications are provided by pharmacy to the clinic beforehand and dispensed to patients by medical staff.

Newly diagnosed patients referred to the service are seen initially by the CNS and return for medical review one to two weeks later, unless the patient is symptomatic in which case they would also be seen by a medic on the same day as the nurse visit.

Patients requiring an STI screen (including all newly diagnosed patients) are referred to the STI clinic (a separate visit). Recommended vaccines are provided in the clinic, but female patients are referred to their GPs or the colposcopy clinic for annual smear tests.

Pregnant patients attend obstetric services separately for their antenatal care.

University Hospital, Limerick

The ID service in UHL provides ambulatory HIV care for approximately 2% of HIV patients in care in Ireland [85].

One clinic per week is held specifically for HIV positive patients in the STI clinic. All patients are seen by an ID consultant and either a clinical nurse manager or RGN. A pharmacist is also present at the clinic to dispense HIV medications. Patients receive STI screening routinely at each visit, recommended vaccines are administered in the clinic and female patients are offered cervical smear testing on an annual basis.

In addition new patients are referred for counselling to external agency part-funded by HSE (GOSHH).

Antenatal patients are scheduled to attend obstetric visits (located separately) on the same day as HIV visits.

St James' Hospital, Dublin

The HIV centre located in the Department of GU Medicine and Infectious Diseases (GUIDE) of SJH is the largest in the country, providing care for over 50% of people with HIV who are attending for care in Ireland [85]. The centre provides care for a greater proportion of complex patients (e.g. older patients, patients with other comorbidities including co-infections, patients with multi drug resistant disease and people who inject drugs) compared to other HIV centres in Ireland. The volume of other resource intensive groups of patients, such as newly diagnosed patients and migrants, also makes the service demands unique at SJH. In addition SJH differs from other centres in that a large proportion (an estimated 50%) of patients do not have a GP, and so use the centre for both secondary and primary care, increasing the demands on clinic staff, in particular doctor and social worker time. Finally the

department operates a significant in-patient programme impacted upon by the out-patient demographic mix and the number of late presenters to HIV care nationally (i.e. transfers from other sites).

To provide appropriate care for the complex patient mix, SJH has a wide variety of staff types (social workers, vaccine nurse, research nurse, health advisors, phlebotomist, nutritionist, data manager) providing on-site support in addition to ID consultants, NCHDs, specialist nurses and pharmacists.

The outpatient department at SJH has an electronic patient record system, enabling instant access to patient chart. While this system has many benefits its use has resulted in increased time spent scheduling and managing clinic appointments (clerical staff) and updating medical notes (medical staff).

Services provided

There are two HIV clinics, one viral hepatitis clinic, one TB/HIV co-infection clinic and one nurse led new diagnosis clinic per week. A vaccination programme is run in parallel, which provides patients with appropriate vaccines as recommended by the National Immunisation Guidelines.

A day-ward service is available for patients that require any procedures as well as acting as an access point to medical care outside clinic hours when necessary.

STI screening is provided as part of routine outpatient visits for men who have sex with men (MSMs) and as required for other patient groups. Cervical smears are offered on-site to female patients on an annual basis. SJH also provides facial fillers (New-fill®) for the treatment of lipodystrophy on-site.

There is also an active research programme at SJH, with a clinical studies unit and dedicated nursing staff.

In addition clinics are provided on location at:

- The Coombe Women and Infants University Hospital (fortnightly clinic providing combined antenatal and HIV care, staffed by GUIDE CNS and Consultant Physician)
- Wheatfield and Clover Hill prisons (weekly clinic staffed by a GUIDE Consultant Physician)
- National Centre for Hereditary Coagulation Disorders (Clinic for HIV positive haemophiliacs, located in NCHCD, bi-monthly clinic run by GUIDE Consultant Physician and CNS)
- Drug treatment centre (Trinity Court) (GUIDE CNS visits DTC once monthly, overseen by GUIDE Consultant Physician)
- Gay Men's Health Service (HSE Sexual Health Clinic for MSMs, two evenings per week, staffed mostly by GUIDE Staff (some allocated, others as agency staff) and GUIDE Consultant Physician as Clinical Director)
- Dublin AIDS Alliance (fortnightly STI screening run by GUIDE ANP)

The Mater Misericordiae University Hospital, Dublin

The HIV service provided by the ID Department of MMUH is the second largest in the country, providing care for approximately 17% of HIV patients in care in Ireland [85].

The patient population attending MMUH is broadly similar to the other centres, although MMUH does provide care for a large cohort of patients who acquired HIV through intravenous drug use in the past and who are also co infected with HCV. More recently most newly diagnosed patients referred to the centre have been MSM, reflecting the increase in HIV diagnoses MSM nationally.

There are three general HIV clinics held per week. Patients are seen by either an ID consultant or a registrar (with consultant input when required). Newly diagnosed patients, and a small proportion of routine patients, are also seen by a Clinical Nurse Specialist. Pharmacists and a social worker are also available on-site during clinic hours. Patients co-infected with hepatitis C virus (HCV) and/or tuberculosis (TB) are treated for their co-infections in the ID clinic. Antenatal patients attend an antenatal-HIV clinic held in the Rotunda Hospital on a monthly basis. General HIV patients are routinely scheduled for outpatient visits every 3-4 months. Patients on treatment for HCV or TB would be seen more frequently for the duration of the treatment.

Patients undergo full STI screening on diagnosis and as required thereafter. Fasting cholesterol and glucose tests are performed annually for each patient, as are cervical smears for female patients. FibroScan® testing is also available on-site for patients co-infected with HCV.

6.4.1.2 Clinic staffing

A summary of the clinic characteristics and staffing levels can be seen in Table 6-5.

Table 6-5. Clinic characteristics and staffing

	Beaumont Hospital		CUH		UCHG		UHL	MMUH	SJH			
Clinic Type	**General ID**	**Nurse led**	**HIV**	**Antenatal HIV**	**General ID**	**Nurse led**	**General ID**	**HIV**	**HIV**	**HCV co-infection**	**New Dx (nurse led)**	**TB (may be nurse led)**
Clinic frequency (number per week/month)	2/week	1/week	1/week	1/month	1/week	1/week	1/week	3/week	2/week	1/week	1/week	1/week
Average number of patients attending per clinic	60	5-10	28	4	20	7	16	40-45	60	45	4	1-2
Proportion of patients attending which are NOT HIV positive	20%	50%	5%	0%	40%	0%	0%	0%	0%	25%	0%	n/a
Please provide the usual number of the following staff working at each clinic												
RGN	1		0.5	0.5			2	2	3-4	2		*
CNS/CNM	2	1	2	1-2	1	1	1	1	1	1	2	1
Consultant	1-2		1		2*		1	3	1-2	1		*

	Beaumont Hospital		CUH		UCHG		UHL	MMUH	SJH			
Clinic Type	**General ID**	**Nurse led**	**HIV**	**Antenatal HIV**	**General ID**	**Nurse led**	**General ID**	**HIV**	**HIV**	**HCV co-infection**	**New Dx (nurse led)**	**TB (may be nurse led)**
Clinical tutor			1	1								
Specialist registrar			1		1				4-5	3-4		*
SHO	1-2		2									
Registrar	1-2				1			2 (+ 1 research)				
Intern	1											
Pharmacist	1		1-2	1-2				2	1	1		
Senior pharmacist							1		2	2		
Chief pharmacist									1	1		
Social worker	1							1	1		2	
Clerical staff	1.5	0.5	0.5	0.5	2	1	2	3	2	2		
Nutritionist									1	1 (part cover)		
Phlebotomy	Done as part of CNS visit		Phlebotomy service	Mid-wife	Phlebotomist + Nurse, on site also do vaccinations			Phlebotomy Nurse (incl RGN above)	1	1		

	Beaumont Hospital		CUH		UCHG		UHL	MMUH	SJH			
Clinic Type	**General ID**	**Nurse led**	**HIV**	**Antenatal HIV**	**General ID**	**Nurse led**	**General ID**	**HIV**	**HIV**	**HCV co-infection**	**New Dx (nurse led)**	**TB (may be nurse led)**
Additional notes					One consultant available solely to advise NCHDs, pharmacy prepares meds prior to clinic			Psych consult may also be required	vaccination clinic runs in parallel (dedicated nurse)			* clinic runs concurrently with ID clinic, patient may be seen by any provider in ID clinic, may be nurse led

6.4.2 Estimated variation in unit costs of HIV outpatient visits

Centre specific flowcharts were generated based on information gathered during the expert interviews (Appendix 9) and these flowcharts were used to generate centre-specific estimates of the staff component of visit unit costs.

The variation in estimated unit costs (staff costs only) of attended outpatient doctor visits is shown in Table 6-6.

Table 6-6. Estimated unit costs of doctor visits by centre (in random order)

	Baseline visit		Routine visit		Antenatal-HIV visit	
Patient on HAART?	No	Yes	No	Yes	No	Yes
Centre A	€199	€269	€118	€168	€144	€194
Centre B	€229	€249	€175	€195	€167	€187
Centre C	€146	€160	€100	€114	€100	€114
Centre D	€295	€339	€116	€163	€126	€167
Centre E	€306	€323	€116	€126	€116	€126
Centre F	€147	€178	€91	€111	€175	€195

There did appear to be some evidence of economies of scale, as the larger centres generally tended to have lower staff visit costs, however this may have simply reflected limitations in the data collection process.

In addition some centres provide nurse-led clinics. As nurse-led clinics were not routinely held in CUH in 2012 they were not included in the original micro-costing study in CUH. To attempt to estimate the additional annual per patient cost of these clinics, the cost of patient-facing and non patient-facing nurse and clerical time (assumed to be the same as a doctor led visit at the centre) was multiplied by the approximate number of visits per year (based on the estimated number of

patients seen per clinic and clinics per year) to generate an annual cost per patient. The estimated cost of nurse-led visits was between €11 and €86 per patient annually (although these estimates appear low, it should be noted that this is an average cost across all patients, but in general only a proportion of patients would attend nurse-led clinics). As nurse visits were not included in the original model (based on micro-costing in CUH) it was not possible to fully incorporate the costs of nurse-only visits into the cost analysis.

6.4.3 National annual non-drug cost of outpatient care per patient

6.4.3.1 Base case analysis and PSA

The estimated annual cost per patient using PSA was €1,127 with a median of €1,111 and an IQR of €1,008-€1,230 (Figure 6-2). Based on this estimate, and assuming there were approximately 3,820 (Chapter 2) people in care in 2012 the approximate cost to the state would have been around €4.31 million.

6.4.3.2 One way sensitivity analysis

One way sensitivity was used to examine uncertainty associated with unit costs of visits (both staff costs and diagnostic testing costs), as well as uncertainty in the proportions of patients in each arm of the model.

Variation of the proportions of patients in each arm of the model had little effect on the estimated average annual cost per patient (1%-2%) (Table 6-7). Variation in the staff costs had a stronger effect (±9%). However, as the costs of diagnostic testing is so uncertain, the diagnostic testing cost was varied by ±60%, and this resulted in a substantial effect on the estimated annual patient cost of about ±34% (Table 6-7).

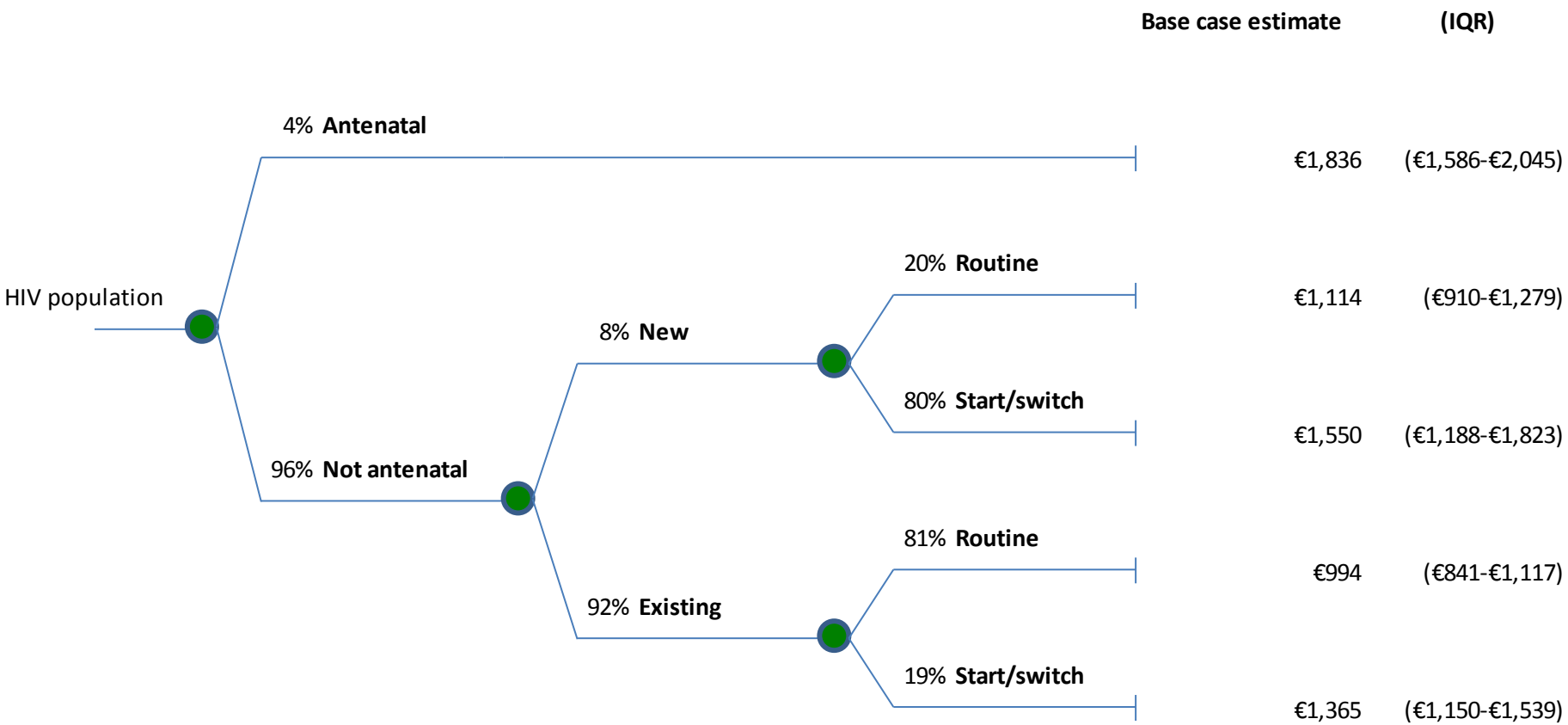


Figure 6-2. Cost model with base case estimates

Table 6-7. Results of one-way sensitivity analysis of national annual non-drug cost of HIV care per patient

	Base case	Low	High	Source of low/high estimate	Annual cost per patient – low estimate	Annual cost per patient – high estimate
Annual cost of visits -staff	€489	-20%	+20%	Microcosting	€1,030	€1,225
Annual cost of diagnostic testing	€639	-60%	+60%	Microcosting	€744	€1,511
% antenatal	4%	2%	7%	95% CI from micro-costing	€1,111	€1,148
% new	8%	5%	11%	95% CI from micro-costing	€1,114	€1,137
New patient, no antenatal, start/switch HAART	80%	63%	97%	95% CI from micro-costing	€1,120	€1,131
Existing patient, no antenatal, start/switch HAART	19%	14%	23%	95% CI from micro-costing	€1,109	€1,139

6.4.3.3 Alternative estimates

The estimated annual per patient costs ranged between €1,063 and €1,358 per centre when centre specific estimated visit costs were used to parameterise the cost model (Table 6-8). The problems of using single-centre estimates is illustrated as using the estimates ranged from 6% below to 20% higher than the weighted average. In reality, the differences between centres could be even greater, as these estimates only attempt to incorporate variation in staff costs and do not take into account differences in utilisation rates, patient characteristics or diagnostic testing costs (unit costs or testing rates) across centres.

Table 6-8. Estimated average annual non-drug patient cost per centre (in random order)

	Average annual non-drug cost per patient
Centre A	€1,267
Centre B	€1,358
Centre C	€1,064
Centre D	€1,256
Centre E	€1,122
Centre F	€1,063

The only routinely available estimate of the cost of an outpatient visit was €130 in 2011 [256], use of this visit cost (inflated to €130.56 in 2012) as a standard cost for all scheduled visit types (staff costs + diagnostic testing costs) resulted in an estimated annual outpatient cost of €537 per patient.

6.4.4 National cost of HAART

The IMS HAART sales data showed that nearly €46 million was spent on HAART in Ireland in 2012. The total spend on HAART drugs has increased rapidly year on year since they became available in 1996 (Figure 6-3). This increase in the annual value of HAART sales reflects the increase in volume of HAART sold (Figure 6-4), rather

than any major changes in average cost per class (Figure 6-5, Figure 6-6). If anything, the average cost of protease inhibitors and multiclass combinations (the drug classes which have been more commonly prescribed in recent years) has fallen slightly (Table 6-9). The increase in volume of HAART being supplied in Ireland is probably due to the combination of increasing prevalence as well as ongoing changes in international recommendations of CD4 thresholds for treatment initiation e.g. the WHO recommended threshold for treatment initiation changed from ≤200 cells/µl to ≤350 cells/µl in 2010 [315], to ≤500 cells/µl in 2013 [40] and recently removed treatment threshold altogether [316].

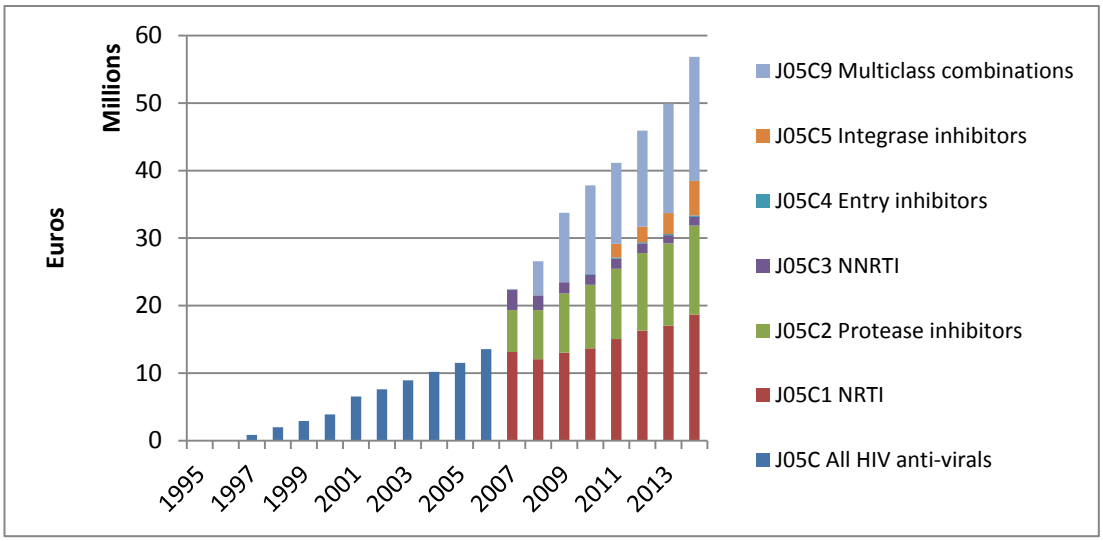


Figure 6-3. Value of HAART sold, by class 1996-2014

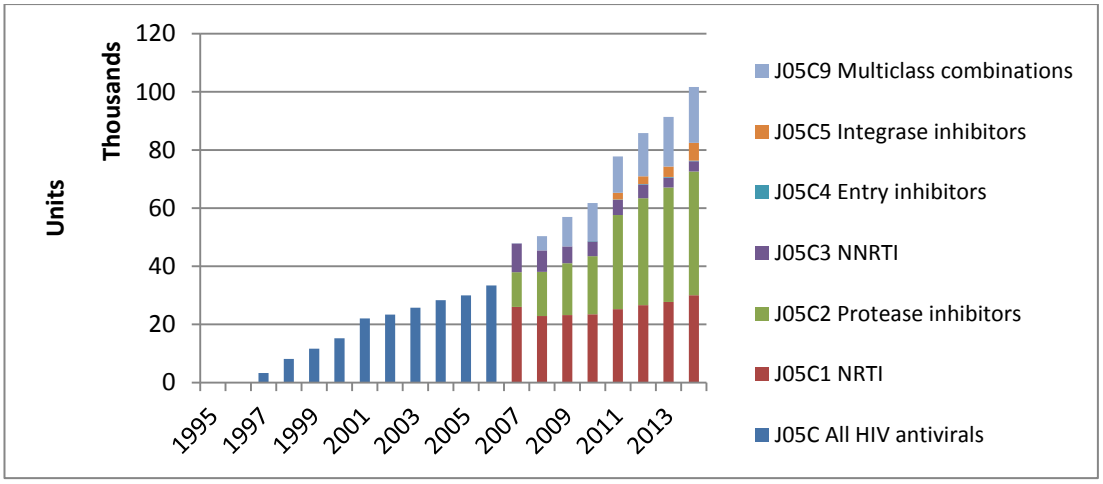


Figure 6-4. Units HAART sold by class, 1996-2014

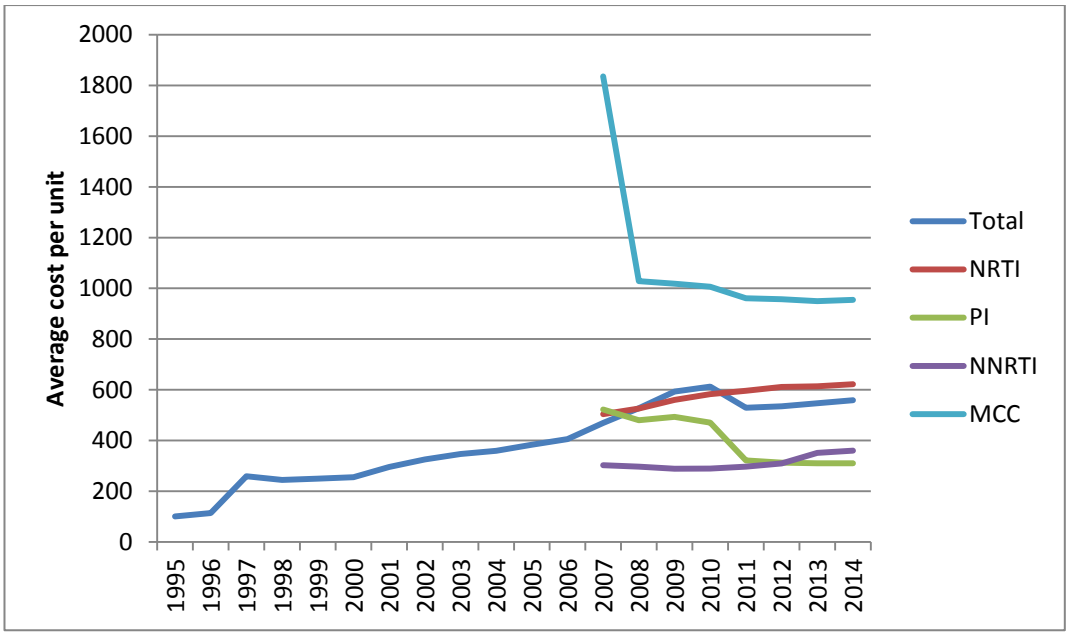


Figure 6-5. Average cost per unit, by class, 1996-2014

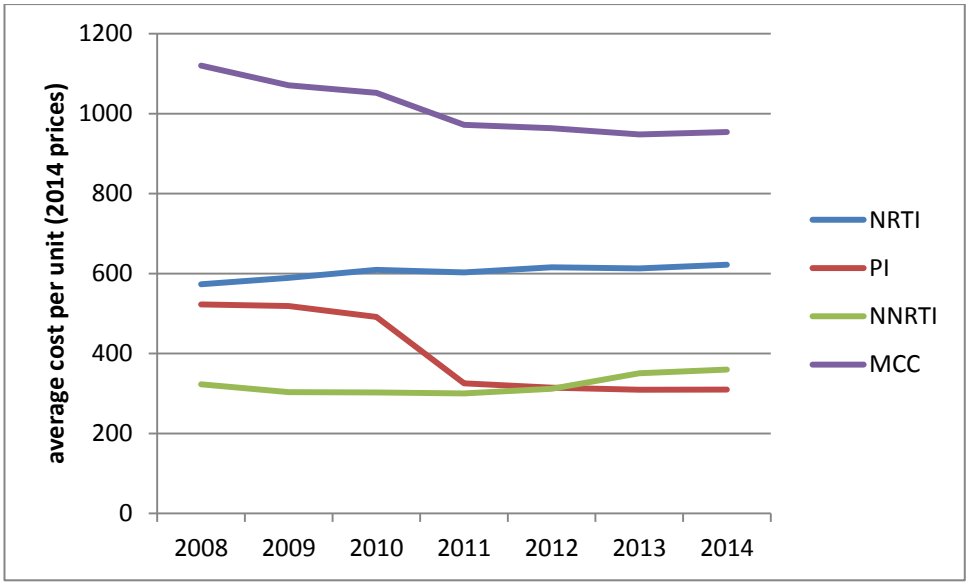


Figure 6-6. Average cost (adjusted to 2014€) per unit 2008-2014

Table 6-9. Proportion of all units, average cost per unit and average cost per unit adjusted to 2014 prices*, by year and drug class

		2008	2009	2010	2011	2012	2013	2014
J05C1 NRTI	proportion of all HAART units	46%	41%	38%	32%	31%	30%	30%
	Average cost per unit	€526	€560	€583	€596	€611	€614	€622
	Average cost per unit (2014 euros)	€573	€589	€609	€603	€616	€613	€622
J05C2 Protease inhibitors	proportion of all HAART units	30%	31%	32%	42%	43%	43%	42%
	Average cost per unit	€480	€493	€470	€322	€312	€310	€310
	Average cost per unit (2014 euros)	€523	€519	€492	€325	€315	€309	€310
J05C3 NNRTI	proportion of all HAART units	15%	10%	8%	7%	5%	4%	3%
	Average cost per unit	€297	€289	€289	€297	€310	€351	€360
	Average cost per unit (2014 euros)	€323	€303	€302	€300	€312	€351	€360
J05C9 Multiclass combinations	proportion of all HAART units	10%	18%	21%	16%	17%	19%	19%
	Average cost per unit	€1,028	€1,018	€1,006	€961	€957	€950	€954
	Average cost per unit (2014 euros)	€1,120	€1,071	€1,052	€972	€964	€948	€954
J05C5 Integrase inhibitors & J05C9 Multiclass combinations	proportion of all HAART units	0%	0%	0%	3%	3%	4%	6%
	Average cost per unit			€966	€873	€871	€870	€845
	Average cost per unit (2014 euros)			€1,010	€883	€878	€869	€845

*Costs adjusted to 2014 prices using the Irish consumer price index for health[257]

6.4.4.1 Comparison to CUH data

Some limited comparisons can be made between IMS data and data on HAART regimens collected in CUH in 2012 as part of the micro-costing study. In CUH, 45% of patients in care and on treatment at the end of 2012 (127/283) were being prescribed a multiclass combination drug. A small proportion of patients were prescribed an additional ARV in combination with a multiclass combination drug. In total 47% of all regimen-months contained a multiclass combination drug, and 24% of all ARV-months dispensed were multiclass combination ARVs. The comparison of the breakdown of number of months of ARVs dispensed in CUH compared to IMS is shown in Figure 6-7.

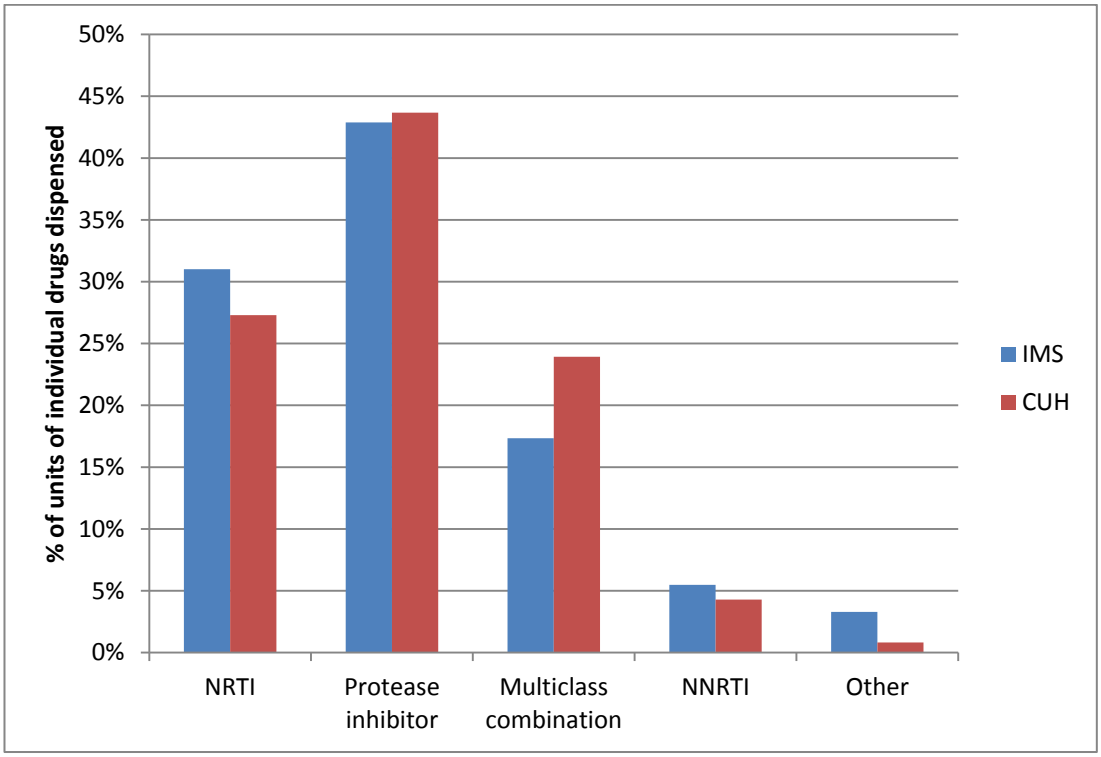


Figure 6-7. Comparison of IMS and CUH ARV data, 2012

6.4.5 Projected costs

The base case estimated cost, in 2012 prices, of providing ambulatory HIV care each year up to the year 2020, can be seen in Table 6-10. The average annual HAART cost per patient as estimated from IMS data was €12,023 in 2012, 25% higher than the estimate from the data collected as part of the micro-costing study in CUH (€9,601). This difference can be ascribed to differences in regimens prescribed in CUH compared to nationally, and also IMS data includes HAART supplied to private patients (and wastage) who are not included in the denominator used to calculate the average cost per year. The use of IMS-based HAART cost data resulted in a base case estimate 23% higher than CUH-based HAART cost data (Table 6-10).

Sensitivity analysis of the estimates found that the estimates were more sensitive to variation of the estimated population than to variation in the annual non-drug costs per patient (Table 6-10).

These projected costs need to be interpreted with caution because of the assumptions underlying the calculations: that the average HAART cost per patient in care; the proportion of patients on HAART; and the ratio of public to private patients will all remain stable over the projected period.

Table 6-10. Sensitivity analysis of estimated projected costs of HIV care in Ireland 2012-2020 by source of estimated drug costs

	2012	2013	2014	2015	2016	2017	2018	2019	2020
CUH drug costs									
Base case	€40,979,638	€42,224,046	€43,779,555	€44,873,776	€45,903,631	€46,847,664	€47,748,787	€48,564,089	€49,422,301
Low visit costs	€39,516,578	€40,716,558	€42,216,532	€43,271,687	€44,264,774	€45,175,103	€46,044,054	€46,830,248	€47,657,820
High visit costs	€42,446,518	€43,735,470	€45,346,659	€46,480,048	€47,546,767	€48,524,592	€49,457,971	€50,302,457	€51,191,389
Low population	€37,868,618	€38,919,928	€40,335,979	€41,204,918	€42,009,493	€42,760,428	€43,446,998	€44,090,657	€44,712,861
High population	€44,348,121	€45,849,993	€47,684,421	€49,025,378	€50,301,969	€51,492,739	€52,672,780	€53,767,001	€54,807,584
IMS drug costs									
Base case	€50,233,458	€51,758,872	€53,665,640	€55,006,952	€56,269,363	€57,426,574	€58,531,184	€59,530,593	€60,582,603
Low visit costs	€48,770,398	€50,251,384	€52,102,617	€53,404,863	€54,630,506	€55,754,013	€56,826,451	€57,796,752	€58,818,122
High visit costs	€51,700,338	€53,270,296	€55,232,744	€56,613,224	€57,912,499	€59,103,502	€60,240,368	€61,268,961	€62,351,691
Low population	€46,419,923	€47,708,635	€49,444,451	€50,509,611	€51,495,870	€52,416,378	€53,257,986	€54,046,993	€54,809,700
High population	€54,362,596	€56,203,613	€58,452,283	€60,096,048	€61,660,913	€63,120,576	€64,567,089	€65,908,401	€67,183,963

6.5 Discussion

Cost-of-illness studies aim to identity all the costs associated with a particular disease, and although they have been criticised for being merely descriptive studies [317-320], they are a useful source of data for decision makers when planning services, particularly preventive services, as well as being useful for drawing the public's attention to a particular health problem, encouraging policy debate, and as a source of input data for cost-effectiveness models [317,321-324].

Using a probabilistic cost model we estimated that the national average annual non-drug cost was €1,127 per patient in 2012. Based on this estimate, at a national level (assuming there were approximately 3,820 people in care in 2012) outpatient visits would have cost in the region of €4.31 million. The value of HAART sales for the same year was €45.93 million, making the total cost to the state of outpatient HIV care of around €50 million in 2012.

While it is notoriously difficult to compare healthcare costs across countries, this estimate of the cost of outpatient care is broadly comparable to that reported in several other developed countries. In the UK the annual non-HAART cost of outpatient HIV care has been reported to be between £628-£1,295 (in 2008) depending on the CD4 strata/AIDS status [161,325], equivalent to €852-€1,756 in Ireland in 2012 (all conversions calculated using CPIs and PPPs available from the OECD). In Italy the annual outpatient cost was estimated to be €1,495 in 2011 (equivalent to €1,677 in Ireland in 2012) [128], while in the US outpatient care (including CD4 and viral load testing) was estimated to range from $915-$1,019 in 2006 [123] (equivalent to €868-€966 in Ireland in 2012). In Canada, outpatient HIV care is estimated to cost around $2,400 annually (Canadian dollars, 2010, equivalent to €1,680 in

Ireland in 2012) [134], while the cost in Sweden was estimated to be €2,520 annually in 2006 (equivalent to €2,388 in Ireland in 2012) [265].

Differences in patient (e.g. patient demographics, epidemiology), clinician (e.g. experience, practice style), hospital/site (e.g. unit costs, resource use, capacity and scale) and health system (e.g. how care is organised nationally/locally, availability of resources to deliver healthcare) factors result in geographic variation in the cost of healthcare (both unit costs and total costs) [163]. The importance of accounting for variation in service delivery between centres was supported by the fact that a difference of up to 20% was found between the estimated base-case adjusted for staff-costs per centre (€1,127 per patient) and individual centres (between €1,063 and €1,358 per patient). The problems with use of cost estimates generated in single-centres has been described in the literature previously [163,310] with larger centre tending to have lower per patient costs due to economies of scale. The variation in annual patient costs between centres showed some evidence of economies of scale, and using a cost estimated in one of the smaller centres (CUH) without taking into account differences in service delivery would be likely to overestimate the cost nationally. However, the use of the published average national outpatient visit cost would have massively underestimated the cost nationally (€537 per patient).

As would be expected the cost of HAART accounts for the overwhelming majority of the cost of care for people with HIV over 90% of the total cost of care (a very similar ratio to that reported in the micro-costing study [284]). Consequently, variations in prescribing patterns between centres are likely to result in considerable variation in the annual per patient cost of providing care between centres. Unfortunately we were not able to evaluate this source of variation in costs across centres as individual patient level HAART data was only available

for CUH, however we were able to make some limited comparisons between the HAART drugs prescribed in CUH in 2012 and those supplied into the market for the same year (data from IMS). A significantly higher proportion of multiclass combination drugs (i.e. Atripla® and Eviplera®) were used in CUH than were used nationally (24% vs 17% of units in 2012, χ^2 $p < 0.001$), and in CUH these multi-class combination drugs cost €273 less per month than the PI based regimens being dispensed (weighted averages €818/month multiclass combination drugs vs €1091 /month for PI based regimens). Without detailed data on HAART prescribing practices and/or local negotiated prices, it is impossible to determine the impact variation in prescribing between centres affects the cost of HIV care.

The data provided by IMS also provides some useful insights into the changing trends in HAART use and cost at a national level. The value of the market in 2012 was nearly €46 million and by 2014 this had increased by 24% to almost €57 million. In reality individual hospitals may negotiate discounts with wholesalers, making the cost to hospitals lower than this. These discount rates are commercially sensitive, making it difficult to establish the actual cost to the health service, a challenge noted previously when performing costing studies in Ireland [326]. However as IMS data is based on what is supplied into the market, it provides a global estimate that encompasses not only HAART supplied to public patients, but also HAART dispensed to private patients, as well as any wastage that may occur within hospitals.

The cost of HAART is likely to continue to increase in the coming years, primarily because of the number new cases continuing to be diagnosed and the increased life expectancy of treated patients. The recent international recommendation to offer HAART to all patients regardless of CD4 count [316], may also result in an increasing in HAART use, although as

the vast majority of patients (between 80%-90% of patients [85,284]) are already on treatment the effect of the removal of the CD4 threshold on the proportion of patients on treatment is likely to be limited by a ceiling effect.

Despite the evidence regarding the scale of variation in cost of providing outpatient HIV care between centres, in the absence of clinic level outcome data we cannot draw any conclusions about the efficiency (i.e. productive efficiency, defined as the maximisation of health outcomes for a given cost or minimisation of cost for a given outcome [327]) of any of the clinics in this study. The efficiency of any service will be influenced by a wide variety of factors both internal and external to the healthcare setting. A review of hospital efficiency in the UK conceptualised different levels of determinants of efficiency (see Figure 6-8). Many of the higher level, external, determinants would be common to all the clinics (e.g. financial incentives) however, internal determinants are likely to vary across hospitals and clinics, for example, the use of technological advances such as electronic patient records, vary between hospitals. Various hospital processes can also be targeted for improved efficiency, such as: reducing unnecessary visits/tests/procedures; reviewing the skill mix of staff; redesigning patient pathways; reducing patient non-attendance at clinic; increasing use of generic medicines etc [328-330].

Efficiency in healthcare is usually measured by a form of benchmarking where the unit(s) with the highest ratio of outputs to inputs are taken as being on the efficiency frontier, and the observed inefficiencies of the remaining units are defined in relation to this (usually using techniques such as Data Envelopment Analysis or Stochastic Frontier Analysis) [330,331]. Although useful these types of analyses are often limited by the data (in particular patient outcome data) that are available. In future, as routine data systems

improve (e.g. hospital activity based costing systems) it may become possible to use that data to identify the most efficient clinics, which in turn could help identify the most efficient way of configuring services.

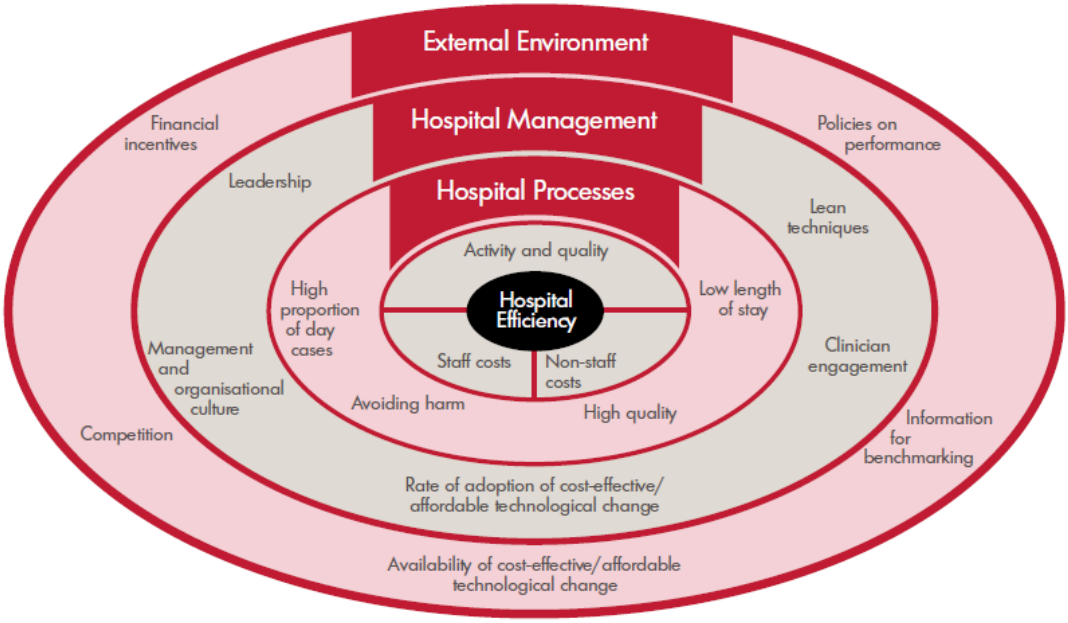


Figure 6-8. Determinants of productive efficiency in hospitals (Source:[330])

Some of the strengths of this study are that it is based on bottom-up micro-costing data, and that uncertainty was addressed using both probabilistic and deterministic methods. We also generated a base case estimate that reflected the effect of variation in service provision across centres on staff costs per visit. In addition the prevalence approach taken by this study is particularly useful for use in the planning of cost containment policies, as it provides a picture of the global burden as well as the major cost components, allowing areas where cost containment policies would have the greatest impact be identified [322].

This study also has several important limitations which need to be recognised.

The annual patient cost estimates were mainly based on data collected in one centre, and as previously mentioned these data may not be generalizable. We attempted to account for variation in service delivery through the generation of centre-specific staff costs per visit type, but were not able to account for any differences (either frequency or unit costs of tests) in diagnostic testing. As the unit costs of diagnostic testing are likely to be subject to economies of scale, the fact that this was not accounted for is likely to have reduced any evidence of economies of scale. In addition the proportions of patients in the various arms of the cost model and the outpatient visit utilisation rates per arm were based on the visit rates in CUH, which are slightly lower than the reported nationally visit rate [85,284], possibly due to differences in characteristics of the patient population attending CUH.

We did attempt to account for differences in service delivery. However, information was collected through expert interviews and may have possibly been subject to reporting bias e.g. staff in busier centres may have underestimated, while staff in centres with fewer patients may have over-estimated the time they spent on HIV. Recall bias may also have been an issue as we collected data in 2014 on service organisation and delivery in 2012. In addition, some of the additional services provided by some centres were not included in the costing (e.g. nurse-led clinics, off-site clinics, contracted services etc). The cost model also only covers care provided in infectious disease outpatient departments, the costs of other services used (even if related to HIV) would not be included. Other costs not included were direct costs to the patient (time, money), intangible costs, and societal costs.

While uncertainty in the cost estimates was addressed as far as possible using both probabilistic and deterministic sensitivity analyses, there may be other, unidentified, sources of uncertainty which remain which may have not been addressed [332].

As hospital-level data was not available on the volume of HAART dispensed by regimen, we had to rely on commercial drug market data. While these data provide an estimate of the total value of the market, as well as some information on the changing patterns of classes of HAART drugs being used, it was not possible to use the data provided to generate information on the regimens being used, which would be more clinically relevant information. Also the sales figures are likely to overestimate the cost to the state as discounts negotiated between individual hospitals and wholesalers are not taken into account.

While data on the cost of providing a service is useful for planning purposes, cost is only one aspect of healthcare quality, and this study did not incorporate data on patient outcomes. Services which are more expensive may be providing better quality care in terms of virological outcomes and/or patient satisfaction. Differences in the characteristics of the patient populations attending each centre were also not addressed.

6.6 Conclusion

The annual cost of outpatient HIV care to the state was estimated to be €51 million in 2012. By 2014 the HAART costs alone had increased to €57 million. In the absence of either a reduction in incidence of new HIV infections or a reduction in annual per patient costs, the cost of caring for people with HIV will continue to increase for the foreseeable future.

7 Discussion

7.1 Introduction

The last in-depth study examining the service use and cost of providing HIV care in Ireland was performed just as HAART became widely available and illustrated the associated decrease in use of in-patient services by HIV patients [143]. At that time, however, it was not clear what the long-term effects of HAART would be. Since then it has become apparent that, if diagnosed in time, patients can survive for decades on treatment [9]. The health consequences of living long term with HIV infection on treatment are only now being seen, with HIV patients at higher risk than the general population for many age related chronic diseases [236,275,276]. It is anticipated that the lifetime costs of HAART treatment, as well as the complex care needs of a population with high rates of multi-morbidity and poly-pharmacy will place increasing demands on the services caring for these patients.

This thesis aimed to study the current use and cost of services and their determinants, to serve as a baseline and to inform future cost-effectiveness analyses for new medications, health care technologies and models of care in the HAART era. This chapter outlines the findings, as well as the main strengths and limitations, of the research carried out. Potential implications of the results of this research for policy makers and service providers are then discussed and some prospective areas for future research proposed.

7.2 Main Findings

The cost of providing care for HIV patients at a national level is a function of the number of patients in care, the volume of resources they use (treatment regimens prescribed, type and frequency of healthcare services attended) and the unit costs of those resources. In this thesis we used a variety of methods to estimate all of these parameters, enabling us

generate national estimates of the current cost of HIV care in Ireland as well as explore the possible impact the changing epidemiology of HIV might have on health services.

7.2.1 Number and age of patients in care

Lack of data (e.g. CD4 count at diagnosis, treatment status and mortality) severely limits any modelling of the prevalence of HIV in Ireland. The only empiric data on the age structure of the HIV population in Ireland comes from a single prevalence survey of patients in care in 2009/2010 [85], and while this study provided an accurate view of the age profile at that time, there are currently no estimates of how the age profile of patients is changing over time.

We attempted to address this through use of simple deterministic models based on routinely available data as well as published estimates of mortality (Chapter 2). The estimated age profile of patients in care in Ireland generated by our model appears to be slightly younger than in other developed countries; for example, in the year 2010, about 15% of patients in Ireland were estimated to be ≥50 years, compared to 21% (≥50 years) in the UK [200], 25% (>55 years) in Australia [141], 28% (>50 years) in the Netherlands [144], and 35% (≥50 years) in the US [202]. Some of these differences are due to variations in methodologies and definitions, but they may also be a result of differences in the historical (e.g. the high proportion of IDU cases in the early years of the Irish epidemic) and current epidemiology of HIV in Ireland (60% of notified cases in Ireland 2002-2013 were <35 years of age compared to 50% of all notifications in the UK in the same period and 44% of notification in the US [194,333]).

The rate of ageing of the population of patients in care as estimated by our model (approximately 0.5 years annually) appears to be very similar that reported by other countries (Figure 2-14).

The overall model estimated that in 2012 18% of patients in care were aged ≥50 years of and that by 2020 this proportion would have increased to 30%. The rate of ageing of patients however is likely to vary across patient subgroups. Unvalidated exploratory modelling by risk category (for cases notified in 2003 and after) estimated that, unsurprisingly, patients notified before 2003 were the oldest group, with 34% aged ≥50 in 2012, increasing to 65% by 2020. For patients notified after the start of 2003 MSMs had the highest proportion aged ≥50 in 2012 (17%) compared to those with a risk factor of other/unknown (15%), heterosexuals (11%) and IDUs (5%), however, by 2020 the estimated proportion of MSMs ≥50 years had only increased to 22%, while the age profile of the other risk groups were estimated to increase much more dramatically (other/unknown from 15% to 28%, heterosexual from 11% to 24% and IDUs from 5% to 22%). This reflects the relatively large number of young MSMs currently being diagnosed in Ireland each year [82].

7.2.2 Current use and cost of HIV care in Ireland

There is currently very little data available on outpatient costs in Ireland despite the fact that outpatient visits are the most frequent type of hospital contact [334] accounting for an estimated 18% of total current hospital healthcare expenditure in Ireland [335]. The national casemix programme does provide an estimate of the average cost of an outpatient visit (€130 in 2011), however this is an overall average and no data are available on the variation of outpatient costs by specialty [256]. Cost data from the UK show that unit costs of outpatient visits vary considerably by specialty and clinic type (min £25- max £1262,

average £103 in 2009/2010) [336]. Given the lack of existing data on outpatient costs in Ireland we examined two different sources of cost data from a single centre (CUH): routine cost data extracted from a newly implemented hospital activity based costing system as well as cost estimates from a bottom-up micro-costing study. We then extrapolated this single centre data, taking into account differences in outpatient service delivery to generate a national estimate of the annual cost of outpatient HIV care.

The estimated cost of HIV outpatient care in CUH, using routine hospital finance data was nearly half (€63 ppm, 95% CI €59-€67 ppm) of the estimate generated by micro-costing (€117 ppm, 95% CI €111-€124 ppm). It would be expected that given the differences in the methodologies used to estimate the costs these two methods would produce differing estimates, however, it should also be noted that the activity based costing system in CUH had not been fully rolled out across all cost-categories at a patient level in 2012. Use of the national average cost of an outpatient visit resulted in an even lower estimated cost (€47ppm, 95% CI €44-€49ppm).

While all centres provide care based on current international guidelines it was anticipated that there would be variations in how that care is provided, and that these variations would affect the cost of providing ambulatory care. When variation in clinical practice across the six clinical centres in Ireland was incorporated into the calculation of non-drug costs the estimated annual cost was €1,127 per patient. This ranged from €1,063 to €1,358 per patient across centres, with some evidence of economies of scale at the larger centres.

The vast majority of the cost of HIV care is due to the provision of HAART and as choice of treatment regimen is influenced by many patient factors as well as clinician preferences [337], it is likely that the patterns of HAART use also differs across centres. As we only had

patient-level data on HAART regimens from CUH is was not possible to adjust for differences in regimens across centres, and instead used wholesaler sales data to estimate the total cost of ARVs at a national level. These data showed the cost of ARVs to be around €46 million in 2012, an average of around €12,000 per patient in care in 2012 (based on the number of patients in care estimated in Chapter 2).

Our final estimate of the cost of care for HIV in Ireland in 2012 was just under €50 million, 90% of this being the cost of HAART (€46 million) with outpatient visits costing an estimated total of €4.3 million.

In addition to HIV care, HIV patients also use a wide variety of other health care services. In our single centre study we found that outpatient ID care accounted for 35% of total non-drug costs (bearing in mind this may be an underestimate) while in-patient care accounted for 47%, outpatient non-ID care 11%, day-case admissions 5% and ED care 2% of total non-drug costs. While it is difficult to compare costs across studies and health systems, a recent systematic review of the economic impact of HIV in selected European countries reported a similar proportion (51%) of non-drug healthcare costs were due to hospitalisation in the UK, although this proportion varied from 20%-77% in the other four countries included (Italy, Spain, Germany and France) [125].

7.2.3 Determinants of the use and cost of HIV outpatient care

The use of healthcare services is determined by a range of patient (sociodemographic and/or clinical) and healthcare related factors [210,211]. In the case of HIV care, as treatment costs account for the vast majority of the total cost of HIV outpatient care, the number of months of HAART combined with the monthly regimen costs are the primary determinants of annual patient costs. Analyses of HIV costs are complicated by this fact (as

analyses using total costs as an outcome are in reality analyses of the total cost of HAART). In order to examine the factors associated with the use and costs of services as opposed to the use and cost of HAART it is necessary to examine the determinants of HAART costs and outpatient care separately.

Age

Despite the widespread concern regarding the increasing costs of caring for an ageing population [24,144,167,172,338,339], there is relatively little data published in the literature which specifically examines the relationship between the use and/or cost of care for HIV patients by age group in developed countries. Studies have either focused on use and have not reported cost data [223,340], or if cost data is reported, it is difficult to interpret as detailed results are not presented by cost category [123,265,288]. Differences in the types of costs (e.g. total [123,265,288] vs HIV-related costs[134,341]) and patients included (e.g. only patients on treatment [341]) also make comparisons difficult.

In terms of the relationship between age and total cost of care for HIV patients (i.e. including non-HIV care) we did not find any significant association between age and total non-drug cost of care (Table 5-10). The evidence in the literature regarding this association is mixed with some studies reporting a positive association with age [123,288] and others finding no difference [265,341]. Although it has been reported that older patients and those with greater levels of co-morbidity use more services and cost more to care for [135,136,223,288,340,341], we did not identify any published data reporting the breakdown of non-HIV (outpatient/ED/in-patient) care use or costs stratified by age group with which to compare our results in any detail. There could be a number of reasons neither use nor cost of non-HIV care did not increase with age in our population. Our study was limited to a

single centre and only included use of hospital resources, patients may have attended primary care or another hospital for their non-HIV care. The older patients in our study may also differ in mean age and/or risk category from other studies. Patients attending CUH may also be healthier than other centres, as less-healthy patients diagnosed and in care before the service was established in 1997 may have been less likely to transfer their care to CUH. In addition, there is currently no nationally co-ordinated approach to routine screening for age-related co-morbidities in HIV patients in Ireland, and it's possible that less chronic disease screening is taking place in Ireland compared to other countries. In general, ongoing resource constraints in the Irish health service mean that chronic disease services have tended to prioritise treatment above screening and prevention.

Our finding that there was no association between older age and total cost of HIV care (i.e. excluding non-HIV care) also contradicts previously published findings [134,341]. In order to identify the source of this difference, one needs to look at differences across cost-categories. A recent analysis by Krentz and Gill (2015) found increased HAART costs appeared to be the primary driver of the increased cost of HIV care reported in the older patients [134]. This was attributed to more HAART use in the older group (better adherence and fewer interruptions) as well as the use of more expensive regimens. In our study older patients also had higher levels of HAART use (they were on HAART for 96% of patient months while younger patients on HAART for 88% of patient months) but in contrast to the Canadian study our patients were on less expensive regimens resulting in a lower mean HAART cost ppm (€833 vs €859). This difference may be due to a variety of factors including: different unit costs in HAART drugs between the countries; differences in prescribing

patterns (due to guidelines or physician preferences); differences in patient characteristics (including resistance rates); or a combination of all of these factors.

Based on the results of our systematic review (Chapter 3), we expected age to be associated with increased use of outpatient services, however the opposite was found to be true in our micro-costing study. Patients ≥50 years had significantly fewer outpatient visits compared to younger patients (0.26 ppm vs 0.37ppm respectively, $p<0.001$), again we attribute this to the particular characteristics of the older patients attending CUH, as the anecdotal view of the clinicians in CUH was that the older patients, many of whom had been attending the centre long-term, were a very engaged group and therefore suitable for less frequent monitoring. Another explanation may be that as the "older" (≥50 years) population in CUH was still relatively young, as the patient population ages we may yet see increases in the use of outpatient services. While our finding that older patients did not have increased outpatient visits or non-drug costs was unexpected, in fact it has previously been reported by several studies that the cost of HIV outpatient care (excluding HAART costs) did not differ significantly by age group [128,134,288].

Other socio-demographic factors

Female gender was the only other socio-demographic factor that was significantly associated with total HIV outpatient costs on multivariate analysis (Table 4-5), this was due to significantly increased HAART costs, as more women were prescribed PI based regimens (until recently PI based regimens were recommended in preference for women of child-bearing potential [342]) which tended to be slightly more expensive than NNRTI based regimens. Although the monthly non-drug cost of HIV care for pregnant women was higher (€179, 95% CI €143-€215) than for non- pregnancy women (€111, 95% CI €101-€121) due to

their increased clinic visits and additional laboratory monitoring, because only a small proportion of women (10%) in our study used joint antenatal-HIV care in 2012, on average women did not have significantly increased costs compared to males (Table 4-4). Women also did not have increased non-drug outpatient HIV costs or increased use of non-ID outpatient, inpatient or ED services (Chapter 5).

Clinical Factors

Clinical severity is the most important determinant of the cost of care for HIV patients [121,123,128,135,343]. As would be expected, clinical severity (as indicated by CD4 category) was also associated with increased use and cost of HIV outpatient care in our cohort (Table 4-5). Patients with lower CD4 counts were also more likely to use of non-ID outpatient services, be admitted as inpatients (both HIV-related/associated and HIV-unrelated admissions) and attend the ED, and their total non-drug cost was significantly higher on multivariate analysis (Table 5-10). The resource-intensive nature of caring for people with very advanced HIV infection was illustrated by the fact that the 2% (n=7) of patients with CD4 counts <50 cells/µl accounted for 61% of all inpatients costs and 31% of the total costs of caring for HIV patients in CUH in 2012. Most of these patients were either recently diagnosed or had issues with treatment adherence/retention in care, highlighting the importance of timely diagnosis and engagement in care.

The clinical benefits of being virally supressed was also reflected in the cost of care as patients on treatment who were not suppressed had significantly higher HIV outpatient costs on multivariate analysis (Table 4-5). While patients categorised as non-stable were five times more likely to have a HIV-related/associated admission and 60% more likely to use non-ID outpatient services (Table 5-5 and Table 5-7).

7.2.4 Strengths and limitations

This section provides an overall summary of strengths and limitations of this thesis. The strengths and limitations of the individual studies included in this thesis have previously been discussed in the relevant chapters.

Strengths

This thesis addresses a timely topic in the field of HIV research as increasing HIV prevalence, the ageing of the patient population and movement towards universal treatment means there is increasing focus on identifying the most efficient care delivery models. We have documented the current level and patterns of resource use, enabling the identification of the main cost drivers, as well as patient and health care service characteristics associated with increased resource use. These data, in addition to estimates of the trends in the size and age breakdown of the patient population, are essential information for the planning of HIV care in Ireland.

This research is also very timely in the context of the current changes in the financing of hospital services in Ireland, as hospital funding moves from a block-grant system to an activity based funding (ABF) programme [258]. Clinicians and providers will need access to data on resource use and costs in order to be able to effectively engage with the ABF programme during the development and implementation of ABF funding in Ireland [344]. This study provides up to date detailed information on the cost and resource use of outpatient HIV care.

Another strength of this research is that a prevalence approach was used for the costing and utilisation studies. Taking this approach allows the ascertainment of the total economic burden of a disease given the particular mix of patients present, and is considered

particularly useful for planning cost containment policies, as information on the major cost components can help identify areas where cost containment policies could have most impact [322]. The alternative incidence based approach involves estimating the lifetime cost of new cases of a disease. Differences in the way future costs are treated by these approaches means that incidence-based cost estimates are generally lower than prevalence based estimates, particularly for chronic diseases, as all costs are present-valued and assigned to the year of disease onset, while a prevalence approach assigns costs to year they occur [322]. Information on lifetime costs of a disease are particularly useful for evaluating the full economic impact of preventative measures, but are less useful for decision makers who need to know what costs are likely to be incurred on an annual basis.

Extensive efforts were made during data analysis to address known limitations in the study methodologies, through the use of generalised linear models, allowing for differences in length of follow-up time, and with selection of family and link functions based on recommended tests. Sensitivity analyses were also performed to explore the impact of uncertainty in the models developed. In addition the issue of generalisability, which is a recognised problem in single-centre costing studies, was addressed through collection of information from the other Irish centres on the most important differences in service delivery, which would be likely to affect the unit costs of visits (staff mix and time), and these variations were incorporated into the estimation of national cost.

Limitations

There were major limitations to the modelling of the numbers of patients in care. In addition to the uncertainty associated with the ages of diagnosis and HIV related mortality, many important factors (such as CD4 count at diagnosis, and proportion of patients on

HAART per year) could not be incorporated into the estimates due to a dearth of Irish data. In addition, as only one prevalence study has been carried out to date there was only one time point of observed data with which to compare the model results. It is possible that it was only co-incidence that the age breakdown of the modelled estimates were not significantly different from the observed values. We were also not able to validate the results of the stratified models as empiric data on the age breakdown by risk group of patients in care notified before 2003 was not available. As the estimated number of cases diagnosed between 2015-2020 was based on the average number of new diagnoses over the previous 5 years (2010-2014) any natural increase in number of cases due to an increase in the size of the general population was not taken into account. While it would have been preferable to base the future estimated number of HIV cases on incidence rates, sufficiently detailed projected population data were not available. The use of numbers as opposed to rates should result in a conservative estimate of the number of new infections. In addition, we assumed that the number of new cases 2015-2020 would be stable, but in reality recent surveillance data shows that the number new HIV cases notified is currently increasing [345].

Although we attempted to estimate the cost of ambulatory HIV care in Ireland using the most accurate methodology (micro-costing), the usefulness of performing costing studies is debated in the literature [317-319,346]. It has been argued that cost-of-illness studies do not provide policy makers with the type of information, needed to make important resource allocation decisions, and that research funding would be better spent on cost-effectiveness/cost utility studies [317]. While we agree that cost data should not be used in isolation for priority setting, information on the economic burden associated with a disease

is useful in a variety of ways, including for the justification of intervention programmes and setting disease research priorities, as well as providing an economic framework for programme evaluation [321].

The perspective and epidemiological approach chosen for the costing study has inherent limitations. As we chose to estimate the cost of ambulatory HIV care from the health service provider perspective, only ID clinic outpatient visits were included in the micro-costing and hospital costs in the utilisation study. No other direct costs (either to the health service or to the patient themselves) or indirect (e.g. societal) costs were included. Data collection was limited to that recorded electronically in the hospital information systems; no data was sought directly from patients. This meant that no data could be collected on patients' co-morbidities or use of health services outside the hospital. There is a paucity of evidence regarding the health service costs of HIV care other than inpatient, outpatient and emergency care [125,131]. A recent study in Germany estimated these costs (including rehabilitation, home care and domestic help) to be around 2% of total direct health care cost of HIV [121].

Although we attempted to account for some of the variation in service delivery, as unit costs depend on the interplay of a wide variety of patient, hospital, health system and societal factors [163] it is likely that there are other unmeasured differences which could result in further variation in unit costs across centres. In addition we did not have access to centre-level data on HAART regimens and had to rely on national data on the volume and value of the ARV market in Ireland. While this data source is comprehensive, the format of the data (based on "units" equivalent to a single pack of a single medication) did not allow analysis of trends in the use of particular regimens over time or of patient or centre level differences.

The proportion of patients on PI-based vs NNRTI based regimens has fluctuated over time as new medications have been introduced into the market [337,347,348]. In the last 10 years the use of fixed dose combinations of drugs has increased [349] and a substantial proportion of patients (25%-27% in the US and Australia [350,351]) are now on single tablet regimens. When data on the proportion of months of single tablet regimens dispensed in CUH was compared to IMS data, CUH appeared to have higher use of single drug regimens (Figure 6-7). Variation in regimen choice by clinic has been reported previously in a study in the UK, where clinic and calendar year were found to be more important in determining the choice of particular regimen than patient factors [337].

Although data on patient outcome (i.e. suppression status) were collected in CUH, no data on patient outcomes were collected at a national level, meaning that differences in efficiency of the variation in models of care could not be evaluated. In any case, the small number of centres providing adult HIV care in Ireland would limit any attempt to evaluate differences between centres in a quantitative manner.

It should also be noted that costing studies reflect current practice, which may differ from best-practice. Centres providing services with fewer resources may appear less expensive on paper, but without information on patient outcomes we cannot say that those services are more efficient, as quality of care is an integral part of the definition of efficiency.

Another limitation, which has been mentioned in the relevant chapters, but which is sufficiently important to warrant a further mention is the issue of generalisability of our results as the centre in CUH where the micro-costing and utilisation studies were performed is relatively small, and has a lower proportion of IDUs than some of the larger Dublin centres. In addition, variation in the patient population means that centres vary in the scope

of care they provide (e.g. SJH provides primary care to approximately 50% of their patients as they either do not have a regular GP or they do not attend their GPs for primary care). The small number of older patients and newly diagnosed patients with advanced disease did not allow in-depth examination of these groups of interest.

7.3 Public health and policy implications

Planning for the care of chronic diseases, as HIV now is, requires information on the underlying trends in patient numbers and demographics as well as information on their resource use and costs. Previous disease specific strategies in Ireland have highlighted the limited information on resource use and costs in Ireland and the importance of such data for the on-going assessment of service delivery models, as well as workforce planning [352,353]. This thesis provides estimates of potential changes in the size of the HIV patient population requiring care, and the aging of that population in Ireland in the near future.

As HIV services worldwide struggle to meet the increasing demands placed on them, various service delivery changes have been proposed in the literature which have the potential to improve efficiency, including several strategies now recommended by the WHO such as task-shifting, decentralisation and integration of care [40]. Despite the fact that evidence regarding their cost-effectiveness is limited these strategies are often promoted for reasons other than cost, such as increasing access to treatment in resource limited settings. Their applicability in other contexts is not currently clear. Other suggested methods of reducing costs, such as reducing the frequency of clinical and/or laboratory monitoring [119], may be more useful in the Irish context, but again the cost-effectiveness of such strategies would need to be rigorously evaluated in terms of both clinical outcome and costs before implementation should be considered.

As HAART is the main driver of the cost of HIV care it offers the greatest scope for cost-savings. Use of generic medications [127,159,160], simplification of regimens [161,268,354], local treatment guidelines and/or centralised procurement [162,355] have all been suggested as means of reducing HIV treatment costs. The results of these strategies are promising in terms of cost savings but further data on the possible clinical impact of such interventions is still needed. The availability of proven strategies to control drug costs will become even more essential as the patient population ages and becomes more treatment experienced, as it appears that the increased cost of HIV care associated with older age may be a result of increased treatment costs [134]. The data in this thesis will be available for use in any HTA of new intervention or service delivery model, as well as for modelling studies.

This research has wider implications in terms of the restructuring of hospital financing in Ireland. It is planned that initially prices will be set based on national average costs, which have the advantage of being relatively straightforward to calculate. Use of average costs should incentivise hospitals with above average costs to drive down their costs to the average costs [258]. However, due to economies of scale the use of average costs tends to underestimate the cost of providing services in smaller centres and overestimate costs in larger centres. Our results show that centre specific costs varied from the estimated average by up to 20%, a difference of that magnitude between the funding of a service and what it actually costs to provide the service could have a detrimental effect on smaller centres under new funding mechanisms, while larger centres might not have any incentive to reduce their costs.

The benefits of clear clinical leadership on patient outcomes have been shown for other chronic diseases, such as stroke and cancer, when care was reorganised based on best

available evidence [352,353]. In the case of cancer, services have been centralised [356], while for stroke care designated stroke units have been established in many acute hospitals, with access to additional speciality services via stroke networks [352,357].

While HIV care is already centralised a nationally coordinated approach, to HIV care through the establishment of a National Clinical Program, would help ensure the quality of care being delivered is standardised and maintained e.g. through the use of agreed key performance indicators; the development of recommendations for the screening/prevention of chronic-diseases in HIV patients; and the introduction of HIV prevention initiatives (e.g. pre-exposure prophylaxis, PrEP). As part of this approach, it is vital that a National Disease Registry be established, to facilitate data collection on key performance indicators, as well as to track of patients' use of services and outcomes (including outcomes of prevention interventions, such as PrEP). Data from such as database would be invaluable for the ongoing monitoring of the quality of HIV care, the planning of HIV services and the evaluation of HIV prevention programmes (e.g. PrEP).

A Nationally Coordinated approach to HIV care in Ireland would also have the potential to reduce drug costs, for example through the development of nationally agreed first line treatment options, centralised procurement and introduction of medicines management schemes that would include the use of generics [162]. In addition, as it is proposed that best-practice based pricing will be introduced in Ireland [258], it will be particularly important to have strong stakeholder involvement (supported by data) in that process. For example, a best-practice tariff introduced in the UK for fragility hip fracture involves a base tariff with an additional payment only if six clinical characteristics of best practice are met. This approach involves not only extensive stakeholder involvement in agreeing the

indicators of “best practice”, but also requires the availability of data on the clinical characteristics of care of interest [358].

7.4 Future research

Historically there have been many gaps in the reporting of the basic epidemiology of HIV in Ireland, with little information available on age at diagnosis during the early years of the epidemic, CD4 count at diagnosis, proportion of patients on treatment, and mortality, all of which have limited the ability to model of the epidemic here. While recognising the difficulty and limitations in carrying out retrospective studies, we feel further research is warranted into these areas, to enable more sophisticated modelling of the HIV epidemic in Ireland, in terms of both number of patients as well as their likely future resource needs (e.g. comorbidities and HAART requirements).

To date, the definition of “older” HIV patients has been 50 years of age. However, as the patient population continues to age and understanding of the metabolic, neurologic and neuropsychiatric changes associated with ageing with HIV improves more nuanced analysis of older patients use and costs of healthcare should be carried out (e.g. breakdown by 50-64 years, 65-74 years, 75+ years).

Further research is also needed to investigate possible methods of improving service efficiency. Qualitative research involving both service users and service providers, would be beneficial in the development of novel service innovations, as well as to assess the acceptability of potential changes prior to their implementation. Development of interventions in conjunction with clinicians, ensuring the clinical independence of the treating clinician and also involving the patients themselves has been highlighted as key in previous studies [162]. There is a lack of data internationally on perceived need (see

Chapter 3), which may be an important factor in patient acceptability of potential service delivery changes e.g. if trying to reduce number of visits. Full economic evaluations of viable innovations should be carried out prior to implementation, to allow the cost-effectiveness of such innovations be assessed in an Irish context.

7.5 Conclusion

The number and age profile of HIV patients in care in Ireland is increasing in line with global trends. Demands on health services will also increase in coming years and health services are under pressure to find innovative ways of improving the efficiency of their services. The cost of providing HIV care is influenced by individual patient factors, but also clinic, hospital and health system factors. The drive to improve efficiency should not negatively impact the quality of care being provided; to ensure this a nationally co-ordinated approach, developed in consultation with care providers and patients, is needed.

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APPENDICES

Appendix 1: Publications

Publications included in this thesis:

- Brennan A. Morley D, O'Leary AC, Bergin CJ, Horgan M. Determinants of HIV outpatient service utilization: a systematic review. AIDS & Behavior. 2015;19(1):104-19.
- Brennan A, Jackson A, Horgan M, Bergin CJ, Browne JP. Resource utilisation and cost of ambulatory HIV care in a regional centre in Ireland: a micro-costing study. BMC Health Services Research. 2015; 15:139
- Brennan A, Horgan M, Jackson A, Browne JP, Bergin CJ. Utilisation patterns and cost of hospital care for people living with HIV in Ireland in 2012: a single centre study. Accepted for publication by the International Journal of STD & AIDS.

AIDS Behav
DOI 10.1007/s10461-014-0814-z

ORIGINAL PAPER

Determinants of HIV Outpatient Service Utilization: A Systematic Review

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Abstract Demands on HIV services are increasing as a consequence of the increased life-expectancy of HIV patients in the highly active antiretroviral therapy era. Understanding the factors that influence utilization of ambulatory HIV services is useful for planning service provision. This study reviewed factors associated with utilization of hospital based HIV out-patient services. Studies reporting person-based utilization rates of HIV-specific outpatient services broken down by patient or healthcare characteristics were eligible for inclusion. The Andersen Behavioral Model was used to organize the information extracted into pre-disposing, enabling and need components. Ten studies were included in the final review. Older age, private insurance, urban residence, lower CD4 counts, a diagnosis of AIDS, or anti-retroviral treatment were associated with higher utilization rates. The results of this review are consistent with existing knowledge regarding HIV patients' use of health services. Little information was identified on the influence of health service characteristics on utilization of out-patient services.

Keywords HIV · Ambulatory care · Health care utilization · Review

Electronic supplementary material The online version of this article (doi:10.1007/s10461-014-0814-z) contains supplementary material, which is available to authorized users.

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Introduction

The emergence of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) infection in the mid-1990s has had profound consequences for both those living with HIV and the healthcare systems providing care for them. A person diagnosed with HIV today can have a near normal life expectancy [1]. A recent modeling study estimated that the median life expectancy of people living with HIV after entry to healthcare is over 40 years [2]. Continuing transmission of HIV, combined with the reductions in mortality and increased life-expectancy resulting from HAART, means that both the overall size and the age profile of the HIV population are increasing. These changes will inevitably increase the demands placed on HIV services worldwide.

Utilization of healthcare services is influenced by many factors which operate at individual, healthcare provider and societal levels. Examination of healthcare utilization patterns can be used to identify sub-groups of patients who are either under- or over-utilizing services. Under-utilization of services has consequences for the patient, as it has been shown that patients not fully engaged in care have poorer outcomes [3], while over-utilization is an inefficient use of health system resources. International guidelines for the

Published online: 08 June 2014

care, management and treatment of HIV patients recommend that patients are monitored 2–4 times per year, depending on the individual needs of the patients [4–6]. However there is still debate on the optimal frequency of monitoring [7, 8]. While quality indicators, such as the recent HIV/AIDS Bureau performance measures [9] have been developed which include measures of visit frequency, these measure the proportion of patients meeting a minimum standard and do not provide information on the volume of care being provided. It is necessary to have information on the volume of resources used by patients, and the most important factors which influence patients' utilization of services, to accurately estimate the consequences of the changing population characteristics on future service demand and cost.

The Behavioral Model was originally developed by Andersen in the 1960s to explain why people use healthcare services [10]. The model initially categorized explanatory factors into three components: predisposing, enabling and need factors. Later versions of the model also incorporated health behavior and outcomes, with feedback loops to reflect the dynamic relationships between outcomes, use of services and explanatory factors [11]. It has been widely used since both as a theoretical framework for explaining why people use health services [12], and as an organizational framework for reviewing determinants of health service utilization in a variety of settings and diseases [13–15].

A previous comprehensive review of HIV healthcare utilization performed by Uphold and Mkanta [16] described some variation in use of out-patient services. However, their review did not focus specifically on outpatient services, was not systematic and many of the articles reporting out-patient utilization pre-dated or were from the early HAART era. Other reviews have focused on specific aspects of HIV care such as retention and engagement [17], cost [18] or use of specific services such as prevention services [19]. To our knowledge no review of the determinants of HIV out-patient utilization has been carried out to date.

The aim of this review was to identify any patient and/or healthcare related factors reported in the literature to be associated with HIV outpatient utilization in the HAART era.

Methods

The methodology for carrying out this review was based on published guidance for conducting and reporting systematic reviews [20–22].

The electronic databases PubMed, EMBASE, EconLit and CINAHL (EconLit and CINAHL via EBSCO) were searched for articles published between 01/01/1997 and 01/03/2013. Keyword searches combined common terms for HIV (human immunodeficiency virus or HIV or AIDS), healthcare (ambulatory care or hospital or out-patient or outpatient), utilization (utilization or utilisation or cost or expenditure), and patient characteristics (patient characteristics or determinants or predictors). An example of the full search strategy can be seen in Supplementary Digital Content 1. In addition, the reference lists of articles which underwent full review were manually searched.

Any article which reported person-based utilization rates, or rate-ratios, of adult hospital-based HIV outpatient services, broken down by patient or healthcare factors were eligible to be included, regardless of study design. Due to the impact of HAART on patterns of healthcare utilization, only articles published since 1997 or reporting data for a time period when HAART was routinely available were reviewed.

Studies were excluded if they reported utilization of outpatient care which was not hospital-based (e.g. community, general practitioner, dental, complementary, prevention or home care services); or was not HIV specific (e.g. included outpatient visits to non-HIV services). Studies solely reporting utilization data of sub-groups of patients with specific co-morbidities (e.g. tuberculosis patients, hemophiliacs) and data on patients participating in clinical trials were excluded unless relevant information was reported on patients receiving usual care. Modeling studies were excluded unless they reported original utilization data. Studies which did not contain original utilization data (reviews/opinion pieces), were not peer-reviewed, or were published only in abstract form or in a language other than English, were also excluded.

Data forms for extraction of study characteristics and quality assessment were developed based on published guidelines [20]. Data was extracted from included articles by a single reviewer (AB) and independently checked for completeness and accuracy by a second reviewer (DM).

Information was extracted on general characteristics as well as analysis and reporting of the study results. The risk of bias (selection, information, other bias), choice of outcome measure, statistical analysis, quality of reporting, generalizability of results, and statements of funding/conflicts of interest were extracted and used to assess the overall quality of each study.

The behavioral model for vulnerable populations was used as a framework for categorizing the results of this review into predisposing, enabling and need factors using traditional and vulnerable domains [23].

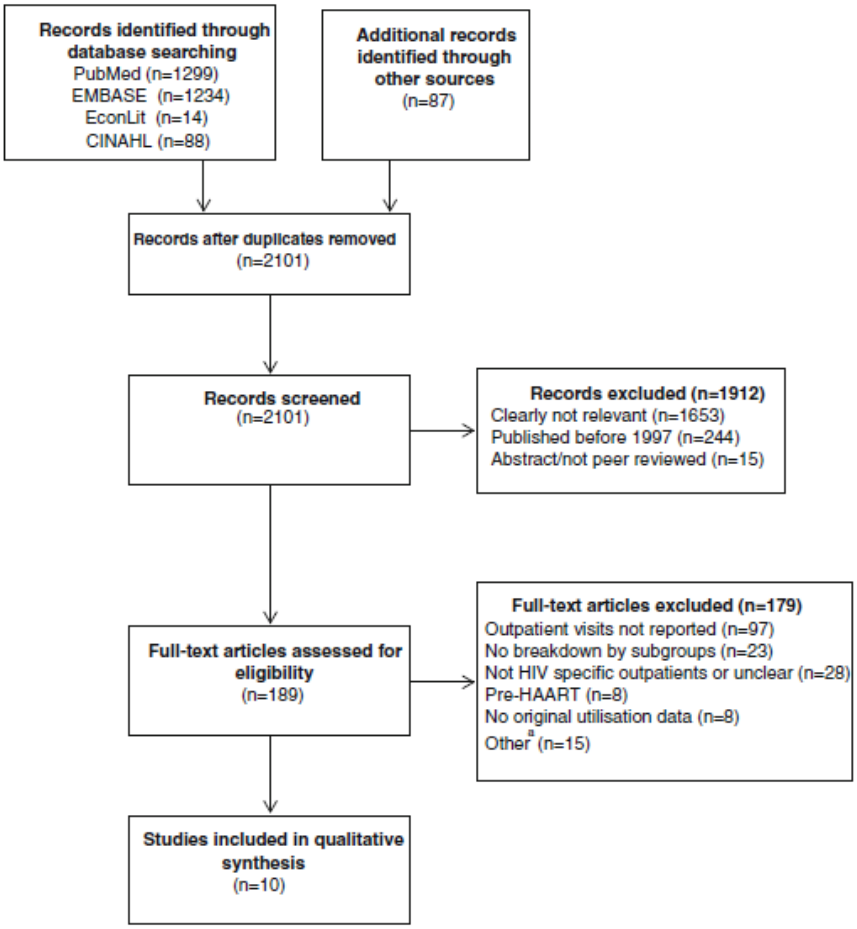


Fig. 1 Flow chart of study selection. [a]Mother-to-child-transmission prevention ($n = 4$), data only relating to a specific subgroup of patients ($n = 3$), not hospital based ($n = 2$), same/overlapping data as another article ($n = 3$), non-English ($n = 1$), clinical trial, no usual care arm ($n = 2$)

Results

Study Characteristics

A total of ten articles were included in the final review. The number of articles excluded at each stage and reasons for exclusion are shown in Fig. 1.

A summary of the study characteristics can be seen in Table 1. Four of the studies included were carried out in the United States (US) [24–27]. Of these, two reported on data collected as part of the HIV Research Network (HIVRN) [24, 26], however as these studies reported data from different years both were retained in this review. The remaining studies were spread across Europe [28–30], Africa [31, 32], and Asia [33].

The quality of seven of the articles reviewed was assessed as average or good, while three were assessed to be of poor quality (Table 2). The main issues affecting methodological quality were a lack of information on the sources of data used, and a low level of statistical analysis. Only two papers reported multivariate analysis [24, 27].

A summary of the results of the studies can be seen in Tables 3 and 4.

HIV Outpatient Use

Predisposing Characteristics

Three of the ten articles included in the review reported utilization rates by the traditional predisposing demographic characteristics of gender, age and ethnicity [24, 27,

Table 1 Characteristics of included studies

Reference	Country	Patient characteristics	Type of study	Data collection	Source of data	Time period of data	Number of patients included	Duration of follow-up:
Bikilla et al. [31]	Ethiopia	No ART or ART, ≥15 years old	Comparison of 2 cohorts overlapping in time	Retrospective	Existing clinic database	Non-ART: Jan 2003–Apr 2004 ART: Aug 2003–Mar 2006	Before: 203 After: 209	Before : up to 15.2 months After: up to 31.2 months
Cook et al. [30]	UK	All attendees	Cohort	Retrospective (every 6 months)	Enhanced HIV surveillance system	Jan 2005–Jun 2006	3,983	Up to 18 months
Fleishman et al. [24]	US	≥18 years old, in longitudinal HIV primary care	Repeat cross-sectional	Retrospective	Existing admin/ hospital database & medical records	2000 2001 2002	13,392 15,211 14,403	1 year
Garattini et al. [29]	Italy	AIDS or non-AIDS by CD4	Cohort	Prospective	Physician collected	Aug 1997–Jul 1998	483	1 year
Howe et al. [27]	US	≥18 years attending care, attended at least 1 appointment subsequent to baseline with laboratory measurements available	Cohort	Prospective	Existing admin/ hospital databases & medical records, patient interview	2001–2007	1,636	Up to 7 years max
Larson et al. [32]	Kenya	1st year of ART, ≥18 years old, not pregnant, files available	Cohort	Retrospective	Medical records	2007–2008	360	12 months
Paton et al. [33]	Singapore	All attendees with at least 3 months of follow-up, who either never had ART, or had only dual or only HAART. Singaporeans or permanent residents	Cohort	Not specified	Existing clinical database	1996–2001	764	Up to 5 years max
Siddiqui et al. [25]	US	Commercial health plan members, 2 medical claims with HIV diagnosis, or 1 medical claim and 1 prescription for ARV, 12 months continuous enrolment	Cohort	Retrospective	Claims database	Jan 2005–Jul 2007	12,189	1 year
Velasco et al. [28]	Spain	All attendees	Cohort	Retrospective	Existing admin/ hospital database	2003–2005	372	Up to 3 years
Wilson et al. [26]	US	≥18 years, in longitudinal primary care	Cross-sectional	Retrospective	Existing admin/ hospital database & medical records	2005	8,824	1 year

Table 2 Quality assessment of included studies

Reference	Assessment of selection bias	Assessment of information bias	SE, SD or 95 % CI of means reported	Multivariate analysis	Other quality issues	Overall assessment of quality
Bikilla et al. [31]	Unlikely	Unlikely	Yes	No	The cohort of patients not on ART was earlier (but overlapping) in time than the cohort on ART. The ART cohort contained a much greater proportion of AIDS patients	Average
Cook et al. [30]	Unclear	Unlikely	Yes	No	Time period used for calculation of rates not clearly reported	Average
Fleishman et al. [24]	Unclear	Unlikely	Yes	Yes		Good
Garattini et al. [29]	Unlikely	Unlikely	Yes	No		Good
Howe et al. [27]	Unlikely	Unlikely	Yes	Yes		Good
Larson et al. [32]	Likely	Unlikely	No	No	Rates specific to individual sites, would not be generalizable	Poor
Paton et al. [33]	Unlikely	Unlikely	No	No	No details given about recruitment of participants	Poor
Siddiqui et al. [25]	Unlikely	Unlikely	Yes	No	Overall generalizability may be an issue as all participants were employees	Average
Velasco et al. [28]	Likely	Unlikely	Yes	No	Time period of utilization data unclear	Poor
Wilson et al. [26]	Unclear	Unlikely	Yes	No		Average

SD standard deviation, *SE* standard error, *CI* confidence interval

30]. Additional predisposing characteristics specific to vulnerable populations reported in the included studies were residency/immigration status [28, 30], and route of infection [24, 27, 30].

Gender

In the studies which reported utilization rates by gender, the majority of participants were male (68–74 %) [24, 27, 30]. Reported rates ranged between 5.46 and 6.44 visits per year [24, 30].

Two of the studies (from the USA and the UK) found no significant differences in utilization rates, although unadjusted female utilization tended to be lower than male [27, 30]. In contrast, the results of a repeat cross-sectional study by Fleishman et al. [24] found utilization rates of females to be greater than males (7–9 % in each of the 3 years reported), with an overall significant increase of 12 % found on multivariate analysis of the 3 year pooled data.

Age Group

The age breakdown of participants in the three studies was broadly similar with the majority of patients being between the ages of 30 and 50 years [24, 27, 30]. Reported rates ranged between 4.12 and 7.4 visits per year [24, 30].

All three articles reported age-groups differently, making comparisons difficult. Fleishman et al. (2005) reported three broad age categories (≤30, 31–49 and 50+ years). Compared to those 30 years and under, utilization rates were 13 % higher in 31–49 year olds and 27 % higher in those aged 50 years and over [24].

Cook et al. (2009) reported data in 5-year age bands, allowing a more detailed pattern of utilization by age

emerge. They found that people in younger and older age groups had higher rates of outpatient visits than people between 20 and 39 years [30]. If their data is re-categorized into the three broad age groups reported by Fleishman et al. (2005), the increased use in the younger age groups is masked, and a similar pattern appears (an increase of 5 and 11 % in the middle and older age groups respectively).

Howe et al. [27] did not report utilization by age group, but reported an increase of 6 % in scheduled attendances with each 10 year increase in age.

Ethnicity

The largest group of patients in both US papers that reported ethnicity were of black ethnicity (47–58 %), with a smaller proportion (27 %) of patients categorized as white [24, 27]. In the UK 67 % of patients were white and 27 % were black Africans [30]. One of the US studies also reported a large proportion of Hispanic participants (18–23 %) [24]. Reported rates ranged between 5.1 and 7.02 visits per year [24, 30].

Compared to whites, black patients tended to have fewer visits [24, 27, 30], but this finding was not significant in any of the studies following adjustment. In contrast, Hispanics were found to have significantly increased use compared to whites [24].

Residency/Immigrant Status

The studies which reported utilization by residency/immigration status found no significant differences in utilization compared to native residents in either the UK [30] or Spain [28], with reported rates ranging between 5.2 and 6.4 visits per year.

Route of Infection

Route of infection provides information on several vulnerable domains including sexual orientation and substance abuse. The categorization of risk groups varied between studies making comparisons difficult, however overall the rates of utilization varied ranged from 4.35 to 7.02 visits per year [24, 30].

The most common routes of transmission were men who have sex with men (MSM) (36–55 %), followed by heterosexual acquisition (32–38 %) [24, 27, 30]. Heterosexuals were consistently found to have lower utilization rates than MSMs [24, 27, 30], although the difference was only significant in one of the studies [24].

People who had acquired their infection through injection drug use (IDU) also had slightly lower utilization rates than MSMs, with a 4 % reduction on multivariate analysis of US data [24]. This was supported by data from the UK although the findings were not significant [30]. Another US study which compared IDUs to non-IDUs found IDUs to have slightly higher utilization rates, but the difference was not significant [27].

Enabling Characteristics

Insurance

Two studies carried out in the US, reported utilization by insurance status, rates varied from 4.28 to 7.38 [24]. Both studies found uninsured patients to have fewer visits than privately insured patients on multivariate analysis, although this difference was not significant in one of the studies [27]. However, the data regarding publically insured patients differed, with one study reporting no difference between public and no/other insurance [27], and the other reporting significant increases of 12 % for Medicaid, and 22 % for Medicare patients compared to those with private insurance [24].

Area of Residence

The variation in categories used again made meaningful comparisons of rates difficult. One study included in this review specifically examined the relationship between rural/urban residence and use of HIV services [26]. They found utilization rates varied significantly by area of residence. Rural residents had the lowest utilization rates (3.95 visits/year), with utilization rates of urban residents and peri-urban residents being 33 % (5.24 visits/year) and 11 % (4.4 visits/year) higher than rural residents respectively. When restricted to patients on HAART, the difference was even greater with urban residents on HAART having utilization rates 45 % (5.83 visits/year) higher than rural residents on HAART (4.02 visits/year). However, these rates were not adjusted for possible confounding variables [26].

The other studies reporting a breakdown by area of residence did not find any significant differences in utilization rates by rural/urban residence [27, 30], or with distance to HIV clinic [27].

Health Service Resources

One study included in this review compared utilization across three sites in one province in Kenya: a government district hospital; a private company hospital; and a mission hospital [32]. All sites receive PEPFAR (US President's emergency plan for AIDS relief) support and provide free out-patient anti-retroviral therapy (ART). The public hospital had the lowest average number of outpatient visits per year (8.3 visits/year), while the private hospital had the

Table 3 Summary of results of included studies

Reference	Predisposing	Enabling	Need
Bikilla et al. [31]			*ART*: patients on ART (AIDS and non-AIDS) had significantly more outpatient visits per year than non-ART patients *AIDS patients*: no significant differences between the number of visits of AIDS patients compared to non-AIDS patients within the groups of patients either on ART or not on ART
Cook et al. [30]	*Gender*: no significant difference in number of visits *Age group*: younger and older age groups had significantly more visits than 25–34 year olds *Ethnicity*: black Africans had significantly fewer visits than whites *Route of infection*: mother to child and MSM had significantly more visits than heterosexuals *Residency*: Asylum seekers and overseas students had significantly fewer visits than UK and other non-UK residents	*Deprivation & urban category*: No significant differences	*Level of ART*: those on quadruple therapy had significantly more visits than those on mono/dual/triple therapy, who had significantly more visits than those not on ART
Fleishman et al. [24]	*Gender*: females had significantly more visits than males *Age group*: number of visits increased significantly with age group *Ethnicity*: Hispanic patients had significantly more visits then whites *Route of transmission*: Heterosexuals and IDUs had significantly fewer visits than MSMs	*Insurance*: compared to those with private insurance those with medicaid and medicare had significantly more visits and those uninsured had significantly fewer visits	*CD4*: number of visits increased significantly as CD4 decreased *VL*: those with VL < 10,000 had a significant, but slight, decrease number of visits compared to those with VL > 100,000 *HAART*: those on HAART had significantly more visits than those not receiving HAART
Garattini et al. [29]			*ADI and CD4 category*: No significant differences
Howe et al. [27]	*Gender*: no significant difference *Age group*: visits increased significantly with age *Ethnicity*: no significant difference *Risk factors*: no significant differences	*Insurance*: no significant differences Urban area: no significant difference *Distance to clinic*: no significant difference *Care first initiated in the study center*: no significant difference	*CD4*: those with CD4 > 350 had significantly fewer visits than those with CD4 < 200 *VL*: no significant difference *AIDS*: those with a clinical diagnosis of AIDS had significantly more visits than those not diagnosed with AIDS *ART*: those on cART had significantly more visits than those not on cART
Larson et al. [32]		*Site*: utilization varied by site, unable to assess if differences were significant	

Table 3 continued

Reference	Predisposing	Enabling	Need
Paton et al. [33]			*CDC stage A*: visits increased from no ART to dual ART to HAART groups (unable to assess significance of differences)
			CDC stage B: More frequent visits in all categories compared to stage A patients (unable to assess significance of differences). Those receiving dual ART had highest utilization, followed by patients on HAART and then patients not on ART (unable to assess significance of differences)
			CDC stage C: similar patter to stage B patients, but rates higher in each category (unable to assess significance of differences)
Siddiqui et al. [25]			*HIV associated weight loss*: those with weight loss had significantly more visits than those without weight loss
Velasco et al. [28]	*Immigrant*: no significant difference		
Wilson et al. [26]		*Area of residence*: utilization increased significantly from rural to peri-urban to urban area of residence for all patients	*HAART patients only*: more frequent visits on average than all patients combined, same pattern of utilization for area of residence (unable to assess significance of differences)

IDU injection drug use, *VL* viral load, *ADI* AIDS defining illness, *(c)ART* (combined) anti-retroviral therapy

highest average number of visits per year (9.5 visits/year). The differences between these rates were not tested statistically, and were not adjusted for any confounding factors. However the median baseline CD4 cell count was highest in the private hospital and lowest in the public hospital.

Source of First HIV Care

Howe et al. [27] found no difference in utilization by people who had initiated their care in their study center compared to those had initiated their care elsewhere.

Need Characteristics

Evaluated Health (AIDS Status/CD4 Count)

Five articles reported utilization rates broken down by some measure of disease severity. The individual measures used varied, however they were all based on some combination of CD4 cell count and/or clinical indicators of AIDS. Utilization rates ranged from 3.3 to 11.4 visits per year [24, 29, 31, 33].

All studies found that as the measure of severity increased, the annual number of outpatient visits also tended to increase [24, 27, 29, 31, 33]. In studies that reported adjusted results, a clinical diagnosis of AIDS was found to be associated with a significant increase in visits (13 % on multivariate analysis), and although categorization of CD4 counts varied across studies, there was a consistent and significant increase in utilization with decreasing CD4 count [24, 27].

One study reported a decrease in outpatient utilization by those with most severe disease (as use of inpatient care increased) [29].

ART/HAART

The reporting of ART varied, with some studies reporting treatment (either ART or HAART) compared to no treatment [24, 27, 31], and others reporting levels of treatment [30, 33].

In general, people on treatment tended to have more visits than patients not on treatment [24, 27, 30, 31, 33], with some evidence that utilization varied less in patients on treatment regardless of disease severity [31, 33]. Two articles reported analyses adjusted for CD4 category, and

Table 4 HIV outpatient visit rates and rate ratios by patient subgroup reported by included studies

Group	Reference	Year(s)	Denominator	Category	Rate (95 % CI)	RR (95 % CI)	RR_{adj} (95 % CI)
Predisposing characteristics							
Gender	Cook et al. [30]	2005–2006	Annualised rate (based on 6 month periods)	Male	6.1 (5.9–6.2)		
				Female	5.8 (5.6–6.1)		
	Fleishman et al. [24]	2000–2002	Calendar year	Male	5.46–5.90		Ref
				Female	5.86–6.44		1.12 (1.09–1.14)
	Howe et al. [27]	2001–2007	Person-months	Female		0.96 (0.92–1.00)	1.01 (0.96–1.07)[a]
Age	Cook et al. [30]	2005–2006	Annualised rate (based on 6 month periods)	0–14	6.8 (5.9–8.0)		
				15–19	7.4 (5.6–9.8)		
				20–24	5.5 (4.9–6.2)		
				25–29	5.6 (5.2–6.0)		
				30–34	5.4 (5.1–5.7)		
				35–39	5.7 (5.5–6.1)		
				40–44	6.5 (6.1–6.8)		
				45–49	6.9 (6.5–7.3)		
				50–54	6.4 (5.8–6.9)		
				55–59	6.2 (5.5–7.0)		
				60+	6.7 (6.0–7.4)		
	Fleishman et al. [24]	2000–2002	Calendar year	18–30	4.12–4.87		ref
				31–49	5.55–6.04		1.13 (1.10–1.16)
				50+	6.39–6.86		1.27 (1.22–1.31)
	Howe et al. [27]	2001–2007	Person-months	per 10 years		1.07 (1.05–1.09)	1.06 (1.04–1.09)[a]
Ethnicity	Cook et al. [30]	2005–2006	Annualised rate (based on 6 month periods)	White	6.1 (6.0–6.3)		
				Black Caribbean	6.5 (5.2–8.2)		
				Black African	5.8 (5.5–6.0)		
				Black Other	6.5 (4.7–9.0)		
				Indian/Pakistani/Bangladeshi	5.5 (4.6–6.6)		
				Other Asian/Oriental	5.5 (4.2–7.1)		
				Other/Mixed	6.0 (5.1–7.1)		
				Unknown	3.6 (2.5–5.1)		
	Fleishman et al. [24]	2000–2002	Calendar year	White	5.28–6.02		ref
				Black	5.10–5.68		1.02 (0.99–1.04)
				Hispanic	6.74–7.02		1.11 (1.08–1.14)
				Other	5.93–6.17		1.04 (0.97–1.12)
				Missing ethnicity	3.59–6.27		0.93 (0.87–1.00)
	Howe et al. [27]	2001–2007	Person-months	African American		0.95 (0.91–0.99)	0.96 (0.92–1.00)[a]

Table 4 continued

Group	Reference	Year(s)	Denominator	Category	Rate (95 % CI)	RR (95 % CI)	RR_{adj} (95 % CI)
Residency/immigration status	Cook et al. [30]	2005–2006	Annualised rate (based on 6 month periods)	UK	6.1 (6.0–6.3)		
				Asylum seeker	5.5 (5.1–6.0)		
				Overseas student	5.2 (4.5–6.0)		
				Other non UK	6.4 (5.8–6.9)		
				Unknown	5.3 (4.8–5.9)		
	Velasco et al. [28]	2003–2005	Study duration	Spaniard	5.8 (SD 4.7)		
				Immigrant	5.6 (SD 4.5)		
Route of transmission	Cook et al. [30]	2005–2006	Annualised rate (based on 6 month periods)	MSM	6.3 (6.3–6.5)		
				IDU	5.3 (4.5–6.2)		
				Heterosexual	5.7 (5.5–6.0)		
				Blood/tissue	5.9 (5.0–7.0)		
				Mother to child	7.2 (6.2–8.3)		
				Other/unknown	4.9 (3.9–6.1)		
	Fleishman et al. [24]	2000–2002	Calendar year	MSM	5.34–5.89		ref
				IDU	6.07–6.38		0.96 (0.93–0.99)
				Heterosexual	5.60–6.12		0.95 (0.93–9.8)
				MSM-IDU	6.62–6.79		1.06 (1.00–1.12)
				Heterosexual-IDU	5.77–6.10		1.04 (0.99–1.09)
				Other	4.35–5.42		0.87 (0.83–0.92)
				Missing	5.35–6.65		0.84 (0.81–0.88)
	Howe et al. [27]	2001–2007	Person-months	Intravenous drug use		1.05 (0.99–1.12)	1.03 (0.96–1.11)
				MSM		1.04 (1.00–1.08)	1.05 (1.00–1.11)[a]
Enabling characteristics							
Insurance	Fleishman et al. [24]	2000–2002	Calendar years	Private	4.53–4.95		ref
				Medicaid	6.36–6.76		1.12 (1.09–1.15)
				Medicare	6.25–7.38		1.22 (1.19–1.26)
				Ryan white/uninsured	4.28–5.32		0.97 (0.94–0.99)
				Missing insurance	2.04–4.42		0.59 (0.55–0.62)
	Howe et al. [27]	2001–2007	Person-months	None/other		ref	ref
				Private		1.07 (1.02–1.12)	1.04 (0.99–1.09)[a]
				Public		1.06 (1.00–1.11)	1.05 (1.00–1.11)[a]

Table 4 continued

Group	Reference	Year(s)	Denominator	Category	Rate (95 % CI)	RR (95 % CI)	$RR_{a\&}$ (95 % CI)
Area of residence	Cook et al. [30]	2005–2006	Annualised rate (based on 6 month periods)	Not urban, least deprived	5.4 (4.8–6.0)		
				Urban, least deprived	6.1 (5.9–6.4)		
				Urban, average deprivation	6.1 (5.8–6.3)		
				Urban, most deprived	5.9 (5.7–6.2)		
	Wilson et al. [26]	2005	Calendar year	Rural	3.95		
				Peri-urban	4.4		
				Urban	5.24		
				Rural (patients on HAART)	4.02		
				Peri-urban (patients on HAART)	4.48		
				Urban (patients on HAART)	5.83		
	Howe et al. [27]	2001–2007	Person-months	Urban area		1.03 (0.98–1.08)	1.02 (0.97–1.07)[a]
				Distance to clinic per 50 miles		0.97 (0.94–1.00)	0.97 (0.94–1.01)[a]
Site	Larson et al. [32]	2007	Patient in care/year	Government District Hospital	8.3		
				Private company hospital	9.5		
				Mission hospital	8.9		
Care first initiated at study site	Howe et al. [27]	2001–2007	Person-months	Yes		1.00 (0.96–1.07)	1.03 (0.98–1.07)[a]
Need characteristics							
AIDS	Howe et al. [27]	2001–2007	Person-months	AIDS		1.17 (1.12–1.22)	1.13 (1.08–1.18)[a]
AIDS and CD4	Garattini et al. [29]	1997–1998	Person-years	ADI	5.9 (5.3–6.7)		
				no ADI, CD4 < 200	6.6 (5.1–8.6)		
				no ADI, CD4 200 - 500	6 (4.8–7.7)		
				no ADI, CD5 > 500	5.6 (4.1–7.9)		
CD4	Fleishman et al. [24]	2000–2002	Calendar years	CD4 < 51	6.36–7.37		1.26 (1.21–1.31)
				CD4 51-200	6.13–6.68		1.15 (1.12–1.18)
				CD4 201-500	5.48–5.92		1.05 (1.04–1.07)
				CD4 > 500	5.07–5.33		ref
	Howe et al. [27]	2001–2007	Person-months	CD4 < 200		ref	ref
				CD4 200–350		0.97 (0.92–1.03)	0.97 (0.92–1.04)[a]
				CD4 > 350		0.90 (0.86–0.95)	0.93 (0.88–0.98)[a]
Viral load	Fleishman et al. [24]	2000–2002	Calendar years	Viral load < 10,000	5.50–5.94		0.97 (0.94–0.99)
				Viral load 10,000–100,000	5.58–6.04		0.98 (0.95–1.01)
				Viral load > 100,000	5.99–6.92		Ref
				Missing	2.32–2.66		0.49 (0.44–0.54)
	Howe et al. [27]	2001–2007	Person-months	Viral load < 400		ref	ref
				Viral load 400–10,000		0.97 (0.92–1.01)	0.99 (0.95–1.04)[a]
				Viral load > 10,000		0.99 (0.94–1.04)	0.99 (0.94–1.04)[a]

Table 4 continued

Group	Reference	Year(s)	Denominator	Category	Rate (95 % CI)	RR (95 % CI)	RR_{adj} (95 % CI)
Anti-retroviral therapy	Cook et al. [30]	2005–2006	Annualised rate (based on 6 month periods)	No ART	4.7 (4.5–4.9)		
				Mono/dual/triple ART	6.4 (6.2–6.6)		
				Quadruple ART	8.1 (7.7–8.5)		
	Fleishman et al. [24]	2000–2002	Calendar years	No HAART	3.77–4.58		ref
				HAART	5.99–6.36		1.39 (1.36–1.42)
				Missing	5.70–6.95		1.02 (0.98–1.07)
	Bikilla et al. [31]	2003–2006	Person-years	No ART	4.6 (4.3–5.0)		
				ART	11.4 (11.0–11.7)		
	Howe et al. [27]	2001–2007	Person-months	cART		1.22 (1.15–1.28)	1.14 (1.08–1.20)[a]
Clinical categories and anti-retroviral therapy	Bikilla et al. [31]	2003–2006	Person-years	Non-ART, non AIDS	4.5 (4.1–4.9)		
				Non-ART, AIDS	5.9 (4.0–7.9)		
				ART, non AIDS	11.4 (11.0–11.8)		
				ART, AIDS	11.3 (10.5–12.1)		
	Paton et al. [33]	1996–2001	Person-years	CDC stage A- no ART	3.33		
				CDC stage A- Dual ART	6.69		
				CDC stage A - HAART	7.73		
				CDC stage B - no ART	5.7		
				CDC stage B - Dual ART	8.24		
				CDC stage B - HAART	7.62		
				CDC stage C - no ART	8.31		
				CDC stage C - Dual ART	9.18		
				CDC stage C - HAART	9.11		
Weight loss	Siddiqui et al. [25]	2005–2007	Person-years	Weight loss	9.7 (SD 12.9)		
				No weight loss	5.9 (SD 5.0)		

SD standard deviation, *ref* reference category, *RR* rate ratio

[a] RRadj also weighted for inverse probability of censoring of drop-out and death

both found patients on HAART attended significantly more frequently (14–39 %) than those not on HAART [24, 27].

Utilization rates also vary by level of ART. In Singapore, Paton et al. [33] found that in patients with less severe disease (CDC stage A) those on dual therapy had less frequent visits than those on triple therapy, but in patients with more severe disease (stage B and C) patients on triple therapy had lower utilization rates than those on dual therapy.

Cook et al. [30] looked at quadruple therapy compared to any other ART (mono/dual/triple) and found that those on quadruple therapy have significantly more outpatient visits, reflecting the fact that quadruple therapy is likely to be a surrogate for HIV drug resistance and be related to an advanced and prolonged clinical history.

Viral Load (VL)

VL is a measure of response to therapy. Two studies reported utilization by VL [24, 27]. One of them found that utilization decreased significantly ($p = 0.05$) as VL decreased, but the difference was small (3 % decrease in those with VL < 10,000 copies RNA/ml compared to VL > 100,000 copies RNA/ml) [24].

Other Indicators of Need

A study of pharmacy and claims data from a large database of commercial health plan members by Siddiqui et al. [25] found that patients with HIV associated weight loss had significantly increased outpatient visits (9.7 visits/year) compared to those with no evidence of weight loss (5.9 visits/year).

Discussion

This systematic review sought to identify determinants of HIV outpatient service utilization, using the behavioral model for vulnerable populations as an organizational framework to present and discuss the findings. The behavioral model has been used to present the results of numerous previous systematic reviews, and the use of a common framework facilitates the comparison with previously published papers across subject areas.

A review of the predictors of healthcare utilization in chronically ill populations using the Behavioral Model concluded that need characteristics (physical and psychological) were the strongest predictors of use, while predisposing and enabling characteristics were of little predictive value in chronically ill populations [15]. In contrast, we found that age was clearly associated with increased use of outpatient services, with evidence from some studies that MSM acquisition, white/Hispanic ethnicity, private insurance and urban residence were also associated with increased utilization rates. The need component of the behavioral model covers both evaluated health and perceived health. As would be expected evaluated health factors (such as CD4 count and/or AIDS diagnosis) were found to be important in determining utilization patterns, with utilization increasing with severity of disease. Patients on antiviral therapy generally tend to attend clinic more frequently than people not on treatment, and their utilization rates also appear to be subject to less variation. The reasons for this are unclear, patients on treatment may simply be scheduled to visit more frequently than those not on treatment, however it is also possible that patients who attend regularly for care could be more likely to be started on treatment (i.e. health behavior influencing outcome), or alternatively, being on treatment may make patients more likely to attend care (i.e. outcome influencing subsequent healthcare use). There was a notable lack of studies on the relationship between utilization of outpatient services and perceived health.

There are several important limitations to this review. The search was restricted to four databases and to articles published in the English language. Non-peer reviewed literature, and articles that were only published in abstract form were not included. In order to allow comparability of results studies were only included if they reported on use of hospital based HIV outpatient clinics which may limit the generalizability of the findings. In addition, the lack of information on patient outcomes and utilization of other (emergency and in-patient) services, make it difficult to identify the health consequences, if any, associated with variation in utilization rates. The majority of studies, regardless of their design, obtained utilization data retrospectively from existing clinical or administrative databases. Retrospective database studies are a useful source of data on healthcare utilization, however there are methodological challenges associated with their use [34]. The studies included in this review generally gave little detail on the databases used, making assessment of the quality of the data sources challenging. The calculation of rates also varied between studies, limiting the interpretation of results to the relative use of services by different subgroups.

Few articles were identified that reported data outside the US and Western Europe, with only two studies from sub-Saharan Africa, one from Southeast Asia, and none from any other region of the world (e.g. Latin America, Eastern Europe/Central Asia, or East Asia). Two of the US studies reported data collected as part of the HIV Research Network (HIVRN), a consortium of sites across the US that provide primary and subspecialty HIV care, with some patient overlap possible. The purpose of the HIVRN is to obtain, analyze and disseminate data on HIV service

utilization in order to provide information for planning and quality assessment of HIV services in the US [35]. No equivalent source of information exists in any other region of the world however, and extrapolation from US data to other regions is difficult, as the structures of healthcare systems as well as the patients cohorts differ considerably. Differences in the categorization of subgroups reported also made comparisons across studies difficult, and can influence the actual rates reported (as was illustrated by the differing age categorizations [24, 30]). Future publications should look to the literature to inform their choice of subgroups, and should report as detailed a breakdown as is practicable, preferably including raw numbers so that if needed, rates could be recalculated for different categorizations.

While little can be concluded about the absolute visit rates reported (Table 4), it is worthwhile noting that the rates were of a similar magnitude across all studies (possibly a reflection of the inclusion criteria for this review), and interestingly, virtually all groups had rates above 4 visits/year, i.e. all groups appear to attend at least as frequently, on average, as is recommended in international guidelines. It is likely that the inclusion criteria of individual studies means that these rates are for people actively engaged in care and have, intentionally or unintentionally, excluded poor attenders which would reduce the averages. In any case, average rates may not by the most appropriate measure of visit data as the data are likely to be very skewed and may be influenced by a minority of high-frequency users (e.g. newly diagnosed/starting or switching treatment). Previous studies have identified subgroups of patients who do not attend as regularly as recommended and/or who have higher missed-appointment rates [3, 36, 37] but this was not reflected in the results of this review. As previously mentioned, this could be a consequence of the inclusion criteria of individual studies, or could be a result of looking at average rates as opposed to proportional measures. At the other end of the spectrum, many groups appear to be attending well in excess of the recommended frequency, although again, due to the limitations of this review the reasons behind this cannot be elucidated.

This review has identified several factors which influence use of HIV services and which should be considered when developing future models projecting the future burden or cost of care for people living with HIV. The increased use of HIV out-patient services associated with older age groups described in this review is consistent with the reported increase in prevalence of co- and multi-morbidity in older HIV patients [38, 39]. As the proportion of older HIV patients rises, the increasing prevalence of co- and multi-morbidity means that demands on health services will multiply accordingly. Anticipating future demands is an essential part of healthcare planning, ensuring adequate provision and allocation of whatever resources are available to provide the most efficient and effective health service possible. In the case of HIV, models predict not only an increase in the total number of patients, but also substantial increases in the proportion of older patients, and in the numbers of patients requiring second-line and subsequent therapies in the coming years [40]. The resource implications of these changes are considerable, not only for the HIV services themselves, but also for the other chronic disease (e.g. oncology [41], cardiac [42], renal [43], and transplant services [44, 45]) and geriatric care [46] specialties that will be seeing more and more HIV-infected patients, and for the co-ordination of care across these multiple providers.

While the changing age profile of HIV patients is the most obvious, and probably the most important, factor several of the other factors are also likely to change in the future, for example increasing health insurance coverage as a result of the affordable health care act in the USA [47], and increasing levels of urbanization [48]. Modeling studies estimating the future cost/burden of HIV should at least consider the possible effects that changing patient, health service and societal changes could have on service use in the future. To date, estimates have been based on current rates of service usage, and have only taken clinical factors, such as severity and ART in account [49, 50]. This review has also highlighted several areas, including patient outcomes, health beliefs and treatment status, where specific research is needed to elucidate their relationship with utilization of outpatient services. Further work on the relationship between patient outcomes and utilization of outpatient services could shed some light on what constitutes under- and over-utilization. Research examining the role of health beliefs in utilization may provide useful insights for the development or implementation patient engagement interventions. Information on the direction and magnitude of the relationship between treatment and utilization may also provide insights into the possible role of treatment as a tool for improving engagement, but is also needed to estimate potential increases in service demand as the numbers of people on treatment increase.

In conclusion, several factors were found to be associated with utilization of outpatient HIV services. As the HIV epidemic evolves these factors may play an increasing role in the demands placed on HIV services, and the most important factors need to be identified and taken into account in future modeling and/or cost-effectiveness studies.

Acknowledgments AB is a Health Research Board PhD Scholar and this work was funded by the Health Research Board in Ireland under Grant No. PHD/2007/16.

Conflict of interest None of the authors have any relevant conflict of interest for this study.

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Brennan et al. BMC Health Services Research (2015) 15:139
DOI 10.1186/s12913-015-0816-1

BMC Health Services Research

RESEARCH ARTICLE Open Access

Resource utilisation and cost of ambulatory HIV care in a regional HIV centre in Ireland: a micro-costing study

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Abstract

Background: It is anticipated that demands on ambulatory HIV services will increase in coming years as a consequence of the increased life expectancy of HIV patients on highly active anti-retroviral therapy (HAART). Accurate cost data are needed to enable evidence based policy decisions be made about new models of service delivery, new technologies and new medications.

Methods: A micro-costing study was carried out in an HIV outpatient clinic in a single regional centre in the south of Ireland. The costs of individual appointment types were estimated based on staff grade and time. Hospital resources used by HIV patients who attended the ambulatory care service in 2012 were identified and extracted from existing hospital systems. Associations between patient characteristics and costs per patient month, in 2012 euros, were examined using univariate and multivariate analyses.

Results: The average cost of providing ambulatory HIV care was found to be €973 (95% confidence interval €938 - €1008) per patient month in 2012. Sensitivity analysis, varying the base-case staff time estimates by 20% and diagnostic testing costs by 60%, estimated the average cost to vary from a low of €927 per patient month to a high of €1019 per patient month. The vast majority of costs were due to the cost of HAART. Women were found to have significantly higher HAART costs per patient month while patients over 50 years of age had significantly lower HAART costs using multivariate analysis.

Conclusions: This study provides the estimated cost of ambulatory care in a regional HIV centre in Ireland. These data are valuable for planning services at a local level, and the identification of patient factors, such as age and gender, associated with resource use is of interest both nationally and internationally for the long-term planning of HIV care provision.

Keywords: HIV, Micro-costing, Cost, Healthcare utilisation, Ambulatory care, Outpatient care

Background

Highly active anti-retroviral therapy (HAART), available since the mid-1990s, has transformed HIV infection into a chronic disease [1]. Nowadays, with timely diagnosis and engagement in care, people living with HIV can have a life-expectancy that approaches that of the general population [2,3]. However, HAART is not a curative treatment and most newly diagnosed HIV patients face the daunting prospect of decades of medication use and regular healthcare visits. It has also become apparent that long term HIV infection and medication use is associated with increased non-AIDS morbidity [1,4,5].

Since HIV testing began in the early 1980s over 6,600 people have been diagnosed with HIV in Ireland [6]. A prevalence study of patients in care found 3,254 patients accessed HIV care in Ireland in the 12-month period from July 2009 to June 2010, with 25% over 45 years of age [7]. Of these patients, 79% were on treatment and 94% of those had a viral load < 500 copies/ml [7], figures that compare favourably with other developed countries [8-10]. In Ireland, as in many other countries, policy makers and clinicians are now faced with the challenge

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of continuing to provide high quality care in the context of increasing demand and within on-going financial constraints.

Data on the use and cost of services are needed to estimate the potential impact the changing HIV epidemiology will have on the health service in Ireland, as well as to support evidence based decisions about new models of service delivery, technologies and medications [11]. It is not generally appropriate to extrapolate costs from studies in different countries due to variation in how health services are provided and organised.

There are two general approaches to costing healthcare: top-down and bottom up. A top-down approach estimates the cost of an individual service on average, usually using routinely available data e. g. average *per diem* costs. Top-down costing studies tend to be relatively quick and easy to carry out, however they are also less precise and cannot provide information on individual factors driving the costs [12]. A bottom-up approach (micro-costing) generates a more precise estimate, but is more difficult to perform. In micro-costing all resources used are identified and then the unit costs of the resources are multiplied by the quantities used [12]. Studies examining the differences between the cost estimates produced by the two approaches have concluded that bottom-up approaches are preferable for estimating cost components which have a large impact on total costs (e.g. labour, drugs), for services where there is wide variation in costs between patients and for centres which are integrated within a larger hospital compared to standalone centres [13-15].

Existing data on the cost of outpatient care in Ireland are limited. The national average cost of an outpatient visit in Ireland was estimated to be €130 in 2011 using a top-down methodology (National Casemix Programme, date of communication 29/09/2013), however no information is available on how this cost may vary across specialties. A previous study looking specifically at the pharmacoeconomics of HIV in Ireland carried out in the early HAART era reported an average outpatient cost of IR£493 per active patient month in 1999 which would be equivalent to €1,184 in 2012 (inflated using the Irish consumer price index for health) [16,17].

Ireland is currently in the process of restructuring its healthcare funding system from one where hospitals are funded based on historical levels of funding adjusted for activity and patient mix to a prospective case based payment system ("Money Follows the Patient") [18]. While it is initially planned to implement this change for in-patient and day-case activity, the new funding system will also encompass outpatient services [18]. It is proposed that prices in the new system will be set initially with reference to average prices, but with a view to implementing best practice prices on an incremental basis [18].

The aim of this study was to estimate the total cost of providing an outpatient HIV service in a single centre in 2012 from the health service provider perspective, and to identify associated patient factors. We also compare our results with other available sources of cost data.

Methods

Ethics

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Cork University Hospital.

Description of service

Cork University hospital (CUH) is one of the largest university teaching hospitals in Ireland, and provides HIV care for the counties of Cork, Kerry, Waterford, and South Tipperary (covering approximately 20% of the Irish population). The infectious disease (ID) department holds two routine outpatient clinics specifically for HIV patients: the main HIV clinic ("HIV clinic") held once a week and a joint ID-maternity clinic ("antenatal-HIV clinic") held once a month in the adjoining maternity hospital. Patients attending the antenatal-HIV clinic attend both obstetric and ID services during their appointment.

Local clinical guidelines, based on international best-practice [19-21], recommend that a CD4 count, viral load (VL), full blood count (FBC) and biochemistry patient profile (renal, liver and bone profiles) are performed every 3–4 months. Additional and/or more frequent testing is recommended at initiation of care and at initiation of HAART until suppression is achieved. Antenatal HIV patients are monitored on a monthly basis.

Study participants

All patients who attended for HIV care in 2012 were identified from a pre-existing clinical database which contains the results of all viral load tests performed in CUH. The database also contains basic demographic and risk factor information on the patients who have attended the public HIV clinic in CUH. Patients who attended the public HIV clinic at least once in 2012 were eligible to be included in the study. Patients who attended for private HIV outpatient care, who did not attend any outpatient appointment in 2012, or who routinely attended another HIV centre for their HIV care were excluded.

For new patients to the clinic in 2012 (newly diagnosed or transferred from another clinic) the date of their first appointment attended or admission was taken as the start date of their care, for all other patients the start date of care was 01/01/2012. Patients were considered to be in care until 31/12/2012 if they used any hospital service (outpatient/in-patient/emergency department) at least once

between 01/07/2012 and 31/12/2012. The files of patients who did not use any hospital service in the last 6 months of 2012 were manually checked, and these patients were censored at the date of their last scheduled appointment where appropriate. Patients who had either a CD4 count < 350 cells/μl or an AIDS defining illness at the time of diagnosis recorded in their medical notes were categorised as late diagnoses.

Resource use

Information on the number and dates of all outpatient appointments and diagnostic tests (laboratory, radiology and cardiology) were extracted from the hospital information system. Data on the total number of months of each HAART regimen dispensed, as well as any relevant start and/or stop dates, were extracted from pharmacy patient files. The medical records of patients with no pharmacy files were cross-checked to confirm the patient did not receive HAART in 2012. In addition, information on the number of doses of prophylactic antibiotics (azithromycin, dapsone, sulfamethoxazole/trimethoprim and pyrimethamine) dispensed to HIV patients was provided by the hospital pharmacy. Diagnostic tests were linked with patient appointments on the basis of matching test and appointment dates. Radiology and cardiology tests, which may not occur on the date of the outpatient appointment where the test was ordered, were linked with the nearest previous outpatient appointment attended.

Costs

A micro-costing study was carried out to estimate the cost of typical HIV outpatient appointments from the service-provider perspective in 2012. Staff routinely involved in providing or supporting the HIV clinic (clerical, nursing, medical, phlebotomy, and pharmacy) were interviewed to assess the HIV-clinic related tasks performed by the staff member and the estimated patient-facing and non patient-facing time involved. Doctors and nurses self-recorded their patient-facing times at six consecutive HIV clinics in March and April 2013 (127/153 appointments timed). Pharmacy staff self-recorded their HIV related patient-facing and non patient-facing time for the month of April, 2013. The accuracy of self-timed doctor patient-facing times was confirmed by independent observation of approximately 50% of appointments. Average costs per appointment were then calculated based on estimated time and salary of relevant staff using recommended national guidelines [22].

Eight basic types of appointment were identified: 1) did not attend scheduled outpatient appointment (DNA), patient was not on HAART at the time ("DNA, not on HAART"); 2) DNA, patient was on HAART at the time ("DNA, on HAART"); 3) attended the HIV-clinic, patient was not on HAART at the time ("Attended HIV clinic, not on HAART"); 4) attended the HIV-clinic, patient was on HAART at the time ("Attended HIV clinic, on HAART"); 5) attended the antenatal HIV-clinic, patient was not on HAART at the time ("Attended antenatal-HIV clinic, not on HAART"); 6) attended the antenatal-HIV clinic, patient was on HAART at the time ("Attended antenatal-HIV clinic, on HAART"); 7) first attended appointment with the ID service for HIV care, patient was not on HAART at the time ("Baseline visit, not on HAART"); and 8) first attended appointment with the ID service for HIV care, patient was on HAART at the time ("Baseline visit, on HAART"). Appointments were categorised as DNA if the patient did not attend their scheduled appointment without cancelling or rescheduling the appointment prior to the start of the clinic they were due to attend. The cost of a DNA appointment was estimated based on the same non patient-facing administrative and pharmacy staff time (where applicable) as attended appointments as well as the time incurred rescheduling an appointment. In general, a patient is considered lost to follow-up if they DNA three consecutive appointments. For the antenatal-HIV clinic appointments only the cost of the care delivered by the ID team was included in the micro-costing.

Unit costs

The unit costs of diagnostic tests were obtained from the finance department of the hospital and the National Virus Reference Laboratory. The monthly costs of antiretroviral medications and prophylactic antibiotics were provided by the hospital pharmacy. In Ireland, the price of all prescribed drugs are set at a national level [23,24], although individual hospitals can negotiate discounts with wholesalers. The number of months of regimens dispensed was used in the calculation of HAART costs to allow for possible wastage due to regimen switching.

The hospital finance department also provided outpatient costs per patient for comparison purposes from a newly implemented activity based costing system. These data were broken down into direct and indirect costs by category (clinical salaries, nursing salaries, non-clinical salaries, imaging, pathology etc.), but contained little information on individual patient characteristics, appointment types or diagnostic tests. Drug costs (with the exception of a few very high cost drugs) were not assigned at a patient level in the hospital activity based costing system in 2012.

Data analysis

All information was entered into a Microsoft Access ® database. Data were analysed using Microsoft Excel® and STATA 12 (College Station, Texas). Weighted average costs per patient month (ppm) were calculated to account for differences in patient lengths of follow-up.

Chi-squared tests were used to test for differences in proportions. Logistic regression was used to estimate the odds ratios of being treated with PI-based regimens compared to NNRTI-based regimens in patients receiving a single type of regimen. Generalized linear models were used to model costs ppm on HAART as they are suitable for modelling cost data, which tend to be skewed, without the need for transformation [25]. The most appropriate family was chosen using the modified Parks test, and the link was chosen using the Pearson Correlation Test, the Pregibon Link Test and the modified Hosmer and Lemeshow test to evaluate power links in increments of 0.1 between 0 and 1 [26].

Unit costs

The unit costs of individual appointment types, common diagnostic tests and regimen types are shown in Table 1.

Sensitivity analysis

To reflect the uncertainty in the estimates of staff time and laboratory costs staff times were varied by 20% and unit costs of diagnostic testing by 60% in a sensitivity

Table 1 Unit costs (in 2012 euros) and frequency of appointment types, most common diagnostic tests and most common HAART regimens dispensed

Cost category	Unit cost	Resource use	Source of cost data
Appointment type	*Staff cost per appointment*	*Number of appointments*	
DNA, not on HAART	€12.68	32	Micro-costing study
DNA, on HAART	€21.25	127	Micro-costing study
Attended HIV clinic, not on HAART	€174.89	89	Micro-costing study
Attended HIV clinic, on HAART	€194.88	997	Micro-costing study
Attended antenatal-HIV clinic, not on HAART	€174.26	2	Micro-costing study
Attended antenatal-HIV clinic, on HAART	€194.25	42	Micro-costing study
Baseline appointment, not on HAART	€244.46	14	Micro-costing study
Baseline appointment, on HAART	€264.45	12	Micro-costing study
Most common diagnostic tests	*Cost per test*	*Number of tests*	
CD4	€47.29	1013	Hospital Finance Dept
Viral load	€92.94	995	National Virus Reference Laboratory
Full Blood Count	€6.79	1036	Hospital Finance Dept
Biochemistry profiles, weighted average cost	€18.63	1042	Hospital Finance Dept
All other tests, weighted average cost	€28.39	1262	Hospital Finance Dept
HAART regimens	*Cost per month*	*Number of months dispensed*	
Efavirenz/Emtricitabine/Tenofovir (NNRTI-based regimen)	€816.61	1515	Hospital pharmacy
Emtricitabine/Tenofovir, Darunavir, Ritonavir (PI-based regimen)	€1,097.51	864	Hospital pharmacy
Emtricitabine/Tenofovir, Atazanavir, Ritonavir (PI-based regimen)	€1,084.84	389	Hospital pharmacy
Emtricitabine/Tenofovir, Lopinavir/Ritonavir (PI-based regimen)	€1,148.79	99	Hospital pharmacy
Emtricitabine/Tenofovir, Nevirapine (NNRTI-based regimen)	€747.98	75	Hospital pharmacy
Lamivudine/Zidovudine, Lopinavir/Ritonavir (PI-based regimen)	€953.16	53	Hospital pharmacy
All other regimens, weighted average cost	€923.70	327	Hospital pharmacy
Prophylactic antibiotics	*Cost per dose*	*Number of doses dispensed*	
Azithromycin	€0.42	330	Hospital Pharmacy
Sulfamethoxazole and trimethoprim	€0.15	2047	Hospital Pharmacy
Dapsone	€0.69	344	Hospital Pharmacy

DNA, did not attend. "Staff cost" is the estimated total patient and non patient-facing staff costs per appointment. Diagnostic tests includes laboratory, radiology and cardiology tests. "Biochemistry profiles" refers to the number and weighted average cost of the following biochemistry profiles: "patient", "ward", "bone", "renal/bone", "patient & lipid", "patient & lipoprotein", "urea, electrolytes & creatinine" and "liver function tests".

analysis. The 20% variation in staff time was based on the approximate width of the confidence intervals of the average doctor and nurse patient-facing times, while the choice of 60% variation for diagnostic testing costs was based on the difference in the weighted average test costs calculated using alternative unit costs which were available for a limited number of the tests.

Results

Study population

In total 326 patients (3659 patient months) were included in this study. The characteristics of the patient population can be seen in Table 2. The majority of patients (59%) were men and the average age of patients was 40 years. Co-infection with hepatitis C virus (HCV) was recorded for 7% of patients, Hepatitis B Virus (HBV) in 2% of patients and both HBV and HCV in 1% of patients. Eight percent (26/326) of patients were new to the service in CUH in 2012, most of whom were newly diagnosed in 2012 (n = 17). The CD4 profile of patients improved with the number of years since diagnosis (Chi-squared test, P = 0.001).

Three patients died in 2012, two of these were considered HIV-related deaths both of which were of people who were newly diagnosed with advanced illness (CD4 < 50 cells/μl) at the time of diagnosis.

Resource use

There were a total of 1315 HIV outpatient appointments scheduled during 2012, with an average of 4.1 (median 4, range 1–15) scheduled appointments per patient and 3.6 (median 3, range 1–11) attended appointments per patient. The frequencies of each type of appointment are shown in Table 1.

In total 304 patients were on HAART for 3272 patient-months, with 3322 months of HAART dispensed in total. The majority of regimens dispensed consisted of a nucleoside reverse-transcriptase inhibitor (NRTI) backbone combined with either a protease inhibitor (PI) or a non-nucleoside reverse-transcriptase inhibitor (NNRTI). NNRTI-based regimens were the most frequently dispensed (164 patients, 1755 months dispensed) followed by PI-based regimens (145 patients, 1477 months dispensed), with a small number of patients being dispensed other regimens types (10 patients, 90 months dispensed). Fifteen percent (n = 45) of patients had more than one regimen prescribed during the study period, most of which were within the same class, although a small number of patients were prescribed regimens from different classes during the study period (n = 15).

Total costs

The overall average cost of providing HIV outpatient care was estimated to be €973 ppm in 2012 (median €940, interquartile range €938-€1008). As the cost of HAART accounted for the majority (88%) of total costs, varying the staff time estimates and unit costs of diagnostic testing did not result in substantial changes to the average costs ppm in the sensitivity analysis, with total costs ppm only varying by about 5% (Table 3). When costs were stratified by whether the patient was on

Table 2 Number and proportion of patients and patient-months by patient characteristics

Characteristics		Patients (%)	Patient months (%)
Patient type	Existing patient	300 (91%)	3506 (95%)
	New patients	26 (8%)	153 (4%)
Gender	Male	192 (59%)	2148 (58%)
	Female	134 (41%)	1511 (41%)
Age	<50 years	284 (87%)	3172 (86%)
	50+ years	42 (13%)	487 (13%)
Risk factor	COHP	133 (41%)	1501 (41%)
	Heterosexual	63 (19%)	721 (20%)
	MSM/Bisexual	95 (29%)	1067 (29%)
	IDU	18 (5%)	185 (5%)
	Other	8 (2%)	96 (3%)
	Unknown	9 (3%)	89 (2%)
Late diagnosis	No	135 (41%)	1535 (42%)
	Unknown	77 (23%)	840 (23%)
	Yes	114 (35%)	1284 (35%)
Years since diagnosis	11+ years ago	95 (29%)	1107 (30%)
	6-10 years ago	107 (33%)	1231 (34%)
	1-5 years ago	100 (30%)	1140 (31%)
	diagnosed in 2012	17 (5%)	105 (3%)
Lowest CD4 count in 2012 (cells/μl)	500+	168 (51%)	1894 (52%)
	350-499	85 (26%)	973 (26%)
	200-349	52 (16%)	581 (16%)
	50-199	14 (4%)	146 (4%)
	<50	7 (2%)	65 (2%)
Treatment and viral load status[b]	On HAART, suppressed	211 (64%)	2469 (67%)
	On HAART, not suppressed	37 (11%)	438 (12%)
	On HAART, unable to determine status	7 (2%)	75 (2%)
	Started/Stopped HAART	49 (15%)	440 (12%)
	Not on HAART	22 (7%)	237 (6%)
Overall		**326 (100%)**	**3659(100%)**

COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/μl at diagnosis or AIDS defining illness at diagnosis. "On HAART" means the patient was on HAART for the entire duration of the study, "suppressed" was defined as all viral loads in 2012 < 50 copies/ml, with one test result of 50–499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml.

Table 3 Average base-case cost, in 2012 euros, per patient month (ppm) and results of sensitivity analysis

	Base case (95% CI)	Lower estimate (95% CI)	Upper estimate (95% CI)
Staff costs ppm (+/− 20%)	€62 (€59-€65)	€50 (€47-€52)	€75 (€71-€78)
Diagnostic test costs ppm (+/−60%)	€55 (€52-€59)	€22 (€21-€23)	€89 (€83-€94)
Total non-drug cost ppm	**€117 (€111-€124)**	**€72 (€68-€76)**	**€163 (€154-€172)**
Total cost ppm (including drug costs)	**€973 (€938-€1,008)**	**€927 (€893-€962)**	**€1,019 (€983-€1,054)**

HAART or not at the time, the average cost ppm not on HAART was €107 (95% CI €65-€150) compared to €1085 (95% CI €1060-€1111) ppm on HAART.

Patient factors

The mean total cost ppm generally differed little across patient groups (Table 4). However, patients who were on HAART for the duration of their time in the study and were categorised as suppressed were found to have lower average total monthly costs compared to those who were not suppressed (mean €1043 ppm compared to €1189 ppm respectively).

HAART accounted for the vast majority of outpatient costs. The unit cost of individual regimens varied from a minimum of €552/month to a maximum of €1600/month. Although NNRTI-based regimens tend to be less expensive than PI-based regimens (the weighted average cost of NNRTI-based regimens in this study was €809/month compared to €1091/month for PI-based regimens), there are many other factors apart from cost which influence regimen choice, including patient (e.g. demographic, behavioural), clinical (resistance, adverse reactions, co-morbidities) and health system factors (drugs available for prescription, clinician preferences). Significantly lower proportions of new patients and newly diagnosed patients received HAART in 2012 compared to existing and previously diagnosed patients (Chi-squared test, P = 0.008 and P =0.017, respectively). While a significantly higher proportion of those diagnosed late (i.e. with a CD4 count <350 cells/μl or an AIDS defining illness at diagnosis) received HAART (Chi-squared test, P = 0.003). On multivariate logistic regression of these three factors late diagnosis was the only factor that remained significant with an odds ratio (OR) of 15.5 (95% CI 2–120). Logistic regression of regimen type (analysis restricted to patients only prescribed PI-based regimens or only prescribed NNRTI-based regimens, n = 283) found women were significantly more likely to be prescribed a PI-based regimen (OR 6.6, 95% CI 3.3-13.2, p < 0.001), while those over 50 years were less likely to be prescribed a PI-based regimen (OR 0.34, 95% CI 0.14-0.85, p = 0.022) when adjusted for risk factor, patient type, years since diagnosis, CD4 < 350 cells/μl and late diagnosis.

The results of multivariate analysis of non-HAART, HAART and total costs ppm on HAART are shown in Table 5.

Comparisons of total costs with other sources of cost data

Patient level costs for the HIV patients included in the micro-costing study were provided by the hospital finance department. The data are activity based costing data, the cost components of which are generated using a top-down methodology. The total number of HIV outpatient appointments in the finance dataset was very similar to the total scheduled number of appointments from the utilisation study (1310 vs 1315) which would be expected given that the finance costs are based on information recorded in the same hospital information system as the utilisation data were extracted from. As the costs of most drugs were not assigned at a patient level in this system in 2012, it was not appropriate to compare drug costs, however the estimated non-drug cost ppm based on the hospital activity-based cost data was €63 ppm (95% CI €59-€67) compared to €117 (95% CI €111-€124) in the micro-costing study. Use of the national average outpatient appointment cost (€130.56 in 2012) would have resulted in an even lower estimate of €47 ppm (95% CI €44-€49 ppm). While our estimate is greater than the estimates generated using routine data, the estimated total cost (€973 ppm) is about 20% lower than the IR£493 per active patient month in 1999 reported by a previous micro-costing study (equivalent to €1,184 in 2012). Although that study was carried out in the early HAART era and the patient population was quite different to the patient population in this study [16].

Discussion

This study reports the results of a bottom-up costing study of routine HIV outpatient care performed in a regional referral centre in the south of Ireland. The total estimated cost of the service in 2012 was €973 ppm, nearly 90% of which was due to the cost of HAART. While it is difficult to compare costs across countries, HAART is reported to account for 60%-80% of the total cost of HIV care (including inpatient care) in many studies in developed countries [27-33].

Despite its cost, HAART is considered a very cost-effective treatment [19,34], and also has the important population-level benefit of reducing onward transmission [35]. HAART also offers the greatest opportunity for reducing costs, for example, in this study the total non-drug spend would have to be reduced by over 35%

Table 4 Costs per patient month (ppm) by patient subgroup

	N	Mean drug cost ppm (95% CI)	Mean non-drug costs ppm (95% CI)	Mean total cost ppm (95% CI)
Patient type				
Existing patient	300	€863 (€829-€897)	€112 (€107-€116)	€975 (€940-€1,010)
New patients	26	€678 (€503-€853)	€253 (€206-€300)	€931 (€732-€1,130)
Gender				
Male	192	€844 (€805-€882)	€117 (€109-€124)	€960 (€921-€999)
Female	134	€873 (€812-€934)	€118 (€108-€129)	€991 (€927-€1,055)
Age group				
<50 years	284	€859 (€821-€897)	€121 (€114-€128)	€980 (€941-€1,019)
50+ years	42	€833 (€773-€894)	€94 (€85-€104)	€928 (€871-€984)
Risk factor				
COHP	133	€878 (€826-€931)	€117 (€106-€127)	€995 (€940-€1,050)
MSM/Bisexual	95	€826 (€769-€884)	€122 (€110-€134)	€948 (€889-€1,007)
Heterosexual	63	€835 (€745-€925)	€113 (€101-€125)	€948 (€856-€1,041)
IDU	18	€931 (€834-€1,027)	€124 (€103-€144)	€1,054 (€942-€1,166)
Other	8	€982 (€733-€1,231)	€92 (€59-€125)	€1,075 (€817-€1,332)
Unknown	9	€697 (€383-€1,012)	€125 (€92-€159)	€823 (€514-€1,132)
Late diagnosis				
No	135	€810 (€748-€871)	€120 (€111-€130)	€930 (€867-€993)
Unknown	77	€868 (€797-€939)	€115 (€103-€126)	€983 (€908-€1,058)
Yes	114	€902 (€862-€942)	€116 (€104-€127)	€1,018 (€974-€1,062)
Years since diagnosis				
11+ years ago	95	€879 (€830-€929)	€102 (€95-€108)	€981 (€930-€1,032)
6-10 years ago	107	€890 (€833-€947)	€107 (€99-€115)	€997 (€938-€1,056)
1-5 years ago	100	€831 (€762-€899)	€130 (€119-€141)	€961 (€889-€1,033)
diagnosed in 2012	17	€581 (€349-€812)	€275 (€208-€342)	€855 (€582-€1,128)
Lowest CD4 count in 2012 (cells/μl)				
500+	168	€888 (€844-€932)	€104 (€98-€110)	€993 (€947-€1,038)
350-499	85	€807 (€734-€879)	€120 (€108-€132)	€927 (€852-€1,002)
200-349	52	€830 (€735-€925)	€129 (€114-€145)	€960 (€861-€1,058)
50-199	14	€839 (€725-€953)	€179 (€115-€244)	€1,018 (€873-€1,164)
<50	7	€903 (€706-€1,100)	€218 (€118-€319)	€1,121 (€842-€1,401)
Treatment and viral load status				
On HAART, suppressed	211	€939 (€915-€964)	€104 (€100-€109)	€1,043 (€1,017-€1,069)
On HAART, not suppressed	37	€1035 (€987-€1,083)	€154 (€134-€175)	€1,189 (€1,133-€1,245)
On HAART, undetermined status	7	€914 (€776-€1,052)	€84 (€55-€113)	€998 (€845-€1,151)
Started/Stopped HAART	49	€660 (€578-€742)	€169 (€141-€197)	€829 (€733-€924)
Not on HAART	22	-	€103 (€79-€128)	€103 (€79-€128)
Overall	**326**	**€856 (€822-€889)**	**€117 (€111-€124)**	**€973 (€938-€1,008)**

COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/μl at diagnosis or AIDS defining illness at diagnosis. "On HAART" means the patient was on HAART for the entire duration of the study, "suppressed" was defined as all viral loads in 2012 < 50 copies/ml, with one test result of 50–499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml.

to save the same amount as could be achieved by a 5% reduction in HAART costs. Possible strategies for reducing HAART costs do exist, such as increased use of generic drugs or less expensive regimens where available and appropriate [36-38], though efforts to reduce drug spend should not come at the cost of increased risk of

Table 5 Results of multivariate analysis of non-HAART, HAART and total costs ppm on HAART

	Non HAART cost ppm on HAART Coefficient[1]	HAART cost ppm Coefficient[2]	Total cost ppm on HAART Coefficient[2]
New patient	−6.555*	−0.03	−0.004
Female	1.464	0.138*	0.139*
Age 50+ years	−3.113*	−0.101*	−0.117*
Risk factor			
COHP			
MSM	1.308	0.033	0.037
Heterosexual	0.32	0.054	0.054
Other/unknown	−0.737	0.05	0.054
Late diagnosis			
No	ref	ref	ref
Unknown	−0.354	−0.012	−0.015
Yes	−0.515	−0.035	−0.04
Years since diagnosis			
11+ years ago	ref	ref	ref
6-10 years ago	−0.267	0.053	0.05
1-5 years ago	1.825	0.041	0.059
diagnosed in 2012	4.504	0.078	0.128
Min CD4 < 350 cells/μl	3.432*	0.02	0.054
On HAART, not suppressed/other	2.051	0.059	0.089*
Constant	31.314	3.896	4.026

1) Generalised linear model with Inverse Gaussian family and link power 0.5. 2) Generalised linear model, with Gaussian family and link power 0.2. * $p < 0.05$. PPM, per patient month. COHP, person from a country of high prevalence with no other identifiable risk factor available. IDU, current/former injecting drug user. Late diagnosis defined as CD4 count < 350 cells/μl at diagnosis or AIDS defining illness at diagnosis. "On HAART" means the patient was on HAART for the entire duration of the study, "suppressed" was defined as all viral loads in 2012 < 50 copies/ml, with one test result of 50–499 copies/ml allowed if previous and subsequent viral load results were < 50 copies/ml. "On HAART, other" includes patients on HAART who were not suppressed or had undetermined status and those who started/stopped HAART in 2012.

poorer outcomes and reduced quality of care [19]. As regimen choice is influenced by patient factors, such as age, gender and risk factor, variation in costs between centres at a national level is likely to be a reflection of differences in patient populations, although clinician preference may also play a role. With time, as more patients switch onto newer treatments, the drug costs are likely to increase unless savings can be made through increased use of generic drugs [36-38] or other rationalisation measures. In any case, further research is warranted into the patient and healthcare factors influencing regimen choice, such as the acceptability and potential impact of a preferred medicine scheme.

The most important factor on multivariate analysis which influenced total costs ppm on HAART was gender, with women being 15% more expensive than men. It was also interesting to note that patients over 50 years of age had significantly reduced costs ppm on HAART. This was due to a combination of older patients tending to be on less expensive NNRTI-based regimens, as well as having fewer scheduled appointments (0.26 ppm compared to 0.37 ppm, $p < 0.001$). The lower appointment rate in older patients contrasts with previous studies which have found older patients have higher utilisation rates [39], and may be a reflection of the particular characteristics of this patient cohort. Late diagnosis has been reported in the literature to be associated with sustained increased healthcare costs [40], in this study there was some evidence that those diagnosed late had higher mean outpatient costs (Table 4), however the differences were not significant using multivariate analysis.

There are several limitations to this study. The data collection was restricted to one year, so changes over time cannot be examined. The usage and cost of other services (inpatient, emergency, and non-ID outpatient care) were not included in this analysis. While the majority of HIV-related care is now provided on an outpatient basis by the ID team, a small minority of patients use a substantial amount of other services [41]. Newly diagnosed patients with low CD4 counts in particular can have very complex care needs, in this study the inpatient costs of two newly diagnosed patients who were diagnosed late and subsequently died were not captured by this micro-costing study. CUH has a smaller proportion of injecting drug users than the national HIV patient population (5% vs 21%), however the population served is similar in terms of age, gender, CD4 count and viral load to the national cohort in care [7]. Diagnostic tests were linked to specific outpatient appointments on date and mis-matching may have occurred which could have led to either an under- or over-estimate of the diagnostic testing ordered by the HIV clinic. Private patients were not included in the study. While private patients do not attend the public outpatient clinic so would not generate appointment costs, the health service provider may incur costs as a result of diagnostic tests and/or HAART. The additional cost of obstetric care for HIV patients (i.e. additional to the three consultant visits that antenatal patients are routinely entitled to [42]) was not included in the cost estimates. As the numbers of women attending antenatal care was very small in this study it was not possible to investigate this fully, but to give an indication of the scale of the possible additional costs the average number of antenatal-HIV appointments attended in this study was 3.2 per woman. This study also does not include the cost of medications prescribed to HIV patients other than HAART and prophylactic antibiotics, as these are dispensed outside the hospital setting, while the total cost of vaccines and

tuberculin dispensed to the HIV clinic was available but could not be assigned at a patient level. The total estimated cost of vaccines and tuberculin in 2012 was €3,734 (including consumables) and even though this is probably an underestimate as patients may be vaccinated in other healthcare settings, overall it is likely to account for a relatively small proportion of the total costs of ambulatory HIV care in this centre.

Conclusions

Accurate cost data are essential for ensuring HIV services are effective, efficient, and equitable and cost information should be used to guide policy, planning and implementation [11]. This is particularly pertinent in the current situation in Ireland, as healthcare funding is undergoing restructuring. We have found that HIV outpatient costs were substantially underestimated by routine hospital cost data, and we feel that this information will be vital for the development of realistic setting of HIV outpatient appointment prices in the new funding system. In addition, as demands on the service increase due to greater numbers of patients and more complex care these cost data will be available for cost-effectiveness evaluations of new drugs, technologies and models of care.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AB, MH and CJB were involved in the study design. AB carried out the data collection with advice from AJ, MH and CJB. AB analysed and drafted the article; all authors contributed to the interpretation of the findings and article revisions. All authors approved the final version of the manuscript.

Acknowledgements

The authors would like to acknowledge and thank all the staff members of Cork University Hospital who participated in the micro-costing study. We would also like to thank Dr Aisling O'Leary for her expert advice on performing costing studies and Andrew Murphy for providing the hospital finance data.

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Received: 20 October 2014 Accepted: 23 March 2015
Published online: 03 April 2015

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Int J STD AIDS OnlineFirst, published on March 21, 2016 as doi:10.1177/0956462416640167

Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–9
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DOI: 10.1177/0956462416640167
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Utilisation patterns and cost of hospital care for people living with HIV in Ireland in 2012: a single-centre study

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Abstract

Data on the pattern and cost of health service use by HIV patients are required for evaluations of the cost-effectiveness of new drugs and technologies as well as being essential for service planning. The aim of this study was to identify the utilisation patterns and cost of hospital care for HIV patients in a single centre in Ireland in 2012. Data on the frequency and non-drug costs of all hospital resources used by HIV patients were extracted from a hospital activity-based costing system. Cost data were analysed using a generalised linear model. A total of 328 patients, 3672 patient months, were included in this study. Patients had a mean of 4.4 scheduled infectious disease outpatient appointments per patient year; 37% of patients also used another outpatient service, 15% in-patient services, 4% day-case service and 18% emergency department services in 2012. Patients with very advanced HIV disease continue to incur a disproportionate amount of the total cost of providing care. This study provides baseline utilisation and cost data for use of both infectious-disease and non-infectious disease hospital services and will be useful for service planning in light of the likely increases in resource demands.

Keywords

Ambulatory care, inpatient, healthcare use, resource use, cost, human immunodeficiency virus

Date received: 22 September 2015; revised: 16 February 2016; accepted: 18 February 2016

Introduction

The epidemiology of HIV infection has changed with the availability of highly active antiretroviral therapy (HAART). Mortality rates in those who initiate treatment early and who are highly adherent approach that of the general population,[1] making HIV infection not only a chronic disease, but one with a relatively long duration and a high per-capita cost compared to other chronic diseases.[2–5]

It has also become apparent that long-term infection with HIV and/or long-term anti-retroviral therapy (ART) is resulting in increasing levels of non-AIDS morbidity,[6] and the prevalence of many non-infectious chronic diseases is higher in people living with HIV than in the general population.[7,8]

Historically, healthcare systems have been designed to provide acute, episodic care and so tend to be less equipped to deal with chronic conditions.[9] The care needs of patients with multiple chronic conditions are particularly complex as these patients tend to have high healthcare utilisation and polypharmacy rates requiring co-ordination across multiple specialties both within and across healthcare providers. While there is currently little consensus in the literature on how to improve care integration, it is clear that in order to provide a service that improves patients outcomes and satisfaction, it is essential that the needs and characteristics of the patient population are taken into account

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when designing services and information management systems.[10,11]

While many studies have published utilisation and/or cost data on all healthcare resources used by HIV patients, fewer studies have reported results broken down by whether the care was HIV related or not. In one study that did, the overall admission rates of HIV patients for non-HIV-related conditions were twice that of HIV-related admissions, with HIV-related admissions being more frequent than non-HIV admissions only in patients with a CD4 count < 75 cells/μL.[12]

We have previously reported utilisation rates and cost of the ambulatory HIV care service.[13] The cost of outpatient care reported in that study (based on micro-costing methodology) was estimated to be between €927 and €1019 per patient month (PPM), 90% of which was due to the cost of HAART. On multivariate analysis, care for males and older people (≥50 years of age) was found to be significantly less expensive. This variation was mostly explained by variations in HAART regimens across groups, although older patients were also found to have significantly fewer appointments.[13] However, that study focussed only on patients' use of HIV clinics and did not evaluate their use of in-patient care, emergency medicine or other outpatient clinics. The aim of this study was to identify HIV- and non-HIV-related hospital utilisation patterns and cost by HIV patients attending a single regional centre in Ireland in 2012.

Methods

We carried out a descriptive study of direct and indirect non-drug healthcare costs in Cork University Hospital (CUH) in 2012. CUH is a tertiary referral centre and was one of only six adult HIV specialist centres which provided HIV care in Ireland in 2012 (the other centres are located in Dublin, Galway and Limerick). HIV care is provided solely by hospital-based practitioners, primary care physicians do not provide specialist HIV care. HIV care provided in the public system is free for Irish residents; however, patients may choose to attend a consultant privately, in which case they pay a consultancy fee for their visit. The catchment area for the HIV service in CUH covers most of the southern region of Ireland (counties Cork, Kerry, Waterford and south Tipperary, a population of approximately 860,000 people). While the total number of people living with HIV in this region is unknown, as the catchment area is mainly rural it is likely that the prevalence of HIV in the region is lower than the 0.1%–0.2% estimated nationally by UNAIDS.[14] It is likely that most patients resident in the region access HIV care in CUH as the nearest alternative HIV centre is located in Limerick (approximately 100 km away). All HIV-positive patients who attended the HIV centre in CUH in 2012 were identified from a pre-existing clinical patient database. Patients who attended the public HIV clinic located in CUH, or who were admitted to CUH in 2012 were eligible to be included in this study. Patients who attended any private HIV outpatient care in 2012 (full or partial year) were excluded. Patients who attended another HIV centre for their routine care (i.e. visitors to the area who attended CUH on a temporary basis) were also excluded. Patients were considered to be in-care from 1 January 2012, or the date of their first visit if they were a new patient, until 31 December 2012. Local clinical guidelines recommended monitoring of HIV patients every three to four months (although a small number of stable patients are monitored on a six-monthly basis). The files of patients who did not attend any HIV clinic appointments in the last six months of 2012 were manually checked, and these patients were censored at the date of their last scheduled visit where appropriate.

Information on admissions (inpatient and day-case, both public and private), outpatient appointments and emergency department (ED) visits in 2012 by the included patients was extracted from the hospital finance system (in 2012 euros). This system is an activity-based costing system ('Power Performance Manager') which uses top-down methodology to generate patient level hospital costs based on hospital accounting and activity data. The cost estimates include both pay and non-pay (e.g. drugs, consumables, utilities, capital expenditure, etc.) costs, based on best accounting practice and in compliance with statutory requirements and Health Service Executive policies and procedures. In 2012, the finance system did not assign drug costs at an individual patient level, so this analysis was limited to non-drugs costs. Data on the cost of appointments with allied health professionals (social workers, dieticians, physiotherapists) were not included in the finance data due to concerns about the completeness of these data. Outpatient visits recorded on this system included 'missed visits' (scheduled appointments which the patient did not attend without cancelling/rescheduling in advance of the clinic) but did not include cancelled appointments. While in general patients' appointments are scheduled in advance, a small number of patients may 'walk-in' to a clinic without an appointment; these visits are recorded on the hospital administration system and were indistinguishable from pre-scheduled appointments in the data extracted.

Ethical approval for this study was obtained from the Research Ethics Committee of CUH.

Utilisation data from a previous micro-costing study[13] were used to cross-check utilisation data and to provide information on whether an outpatient visit was attended or missed. In-patient diagnoses are coded

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using the International Classification of Diseases 10th revision Australian Modification.[15] Up to 30 diagnoses codes can be recorded for each admission. Diagnoses codes for each in-patient episode were reviewed independently by two infectious-disease consultants (AJ and CB), and categorised subjectively as 'HIV related', 'HIV associated' or 'unrelated to HIV'. HIV-related diagnoses were diagnoses that were known to be related to HIV infection (e.g. candidal oesophagitis, adverse reactions to antiviral medication, Kaposi sarcoma), HIV-associated diagnoses were diagnoses for conditions associated with HIV infection (e.g. anal carcinoma), or diagnoses which were possibly related to the underlying HIV infection but which could not be definitely attributed to HIV infection (e.g. unspecified acute lower respiratory tract infection in a virally suppressed patient with a high CD4 count). Episodes where categorisations differed or were not possible to determine on the basis of diagnoses codes alone were re-checked by the consultant in CUH (AJ) in conjunction with a Clinical Nurse Specialist and patient notes. Admissions which occurred within one day of an ED visit were assumed to be linked to that ED visit. In-patient episodes admitted and discharged on the same day were given a length of stay of one day. The CD4 counts reported are the minimum CD4 counts recorded in 2012.

All information was entered into a Microsoft Access® database and analysed using Microsoft Excel® and STATA 12 (College Station, Texas). Mean numbers of appointments per year were calculated weighted by the number of months in care. Differences in proportions were tested using Chi-squared tests. As patients had different length of follow-up during which an episode of care could happen, Chi-squared tests for differences in proportions were limited to the sub-group of patients who were in care for 12 months ($n=287$). Differences in mean costs PPM were tested using either Wilcoxan rank-sum or Kruskal–Wallis rank tests. A binomial generalised linear model was used to test the association between HAART status and missed infectious disease outpatient visits, taking into account length of follow-up and patient clustering. Multivariate analysis of cost data was performed using a generalised linear model (inverse Gaussian family, identity link). The family was selected using a modified Parks test, while the link was identified by evaluating the results of the Pearson, Pregibon and modified Hosmer and Lemeshow tests for power links between 0 and 1 in increments of 0.1.[16]

Results

Description of cohort

A total of 328 patients (3672 patient-months) were included in the study. The characteristics of the patient cohort have been reported previously.[13] The majority of patients (59%) were male, and the average age was 40 years. Thirteen percent ($n=42$) were ≥50 years of age. Most patients had a minimum CD4 count in 2012 >350 cells (77%) and were on HAART for their entire study period (79%), a further 14% received some HAART in 2012, most of whom were patients who initiated HAART in 2012. A small proportion of patients were co-infected with hepatitis C (7%), hepatitis B (2%) or with both hepatitis B and C (1%). Three patients died, two of these were newly diagnosed in 2012 and died of HIV-related causes.

In total, 61 patients were excluded. Limited data were available on the age and sex of excluded patients. Excluded patients were significantly older (mean 47 years vs 40 years, t-test $p<0.0001$) and more likely to be male (77% vs 59%, Chi squared $p=0.005$).

Outpatient care

Infectious disease. There were 1338 infectious-disease outpatient appointments scheduled in the 3672 patient months in 2012 giving an average of 4.4 scheduled visits per patient year (median 4, interquartile range 3–5). While some of these appointments may have been for infectious diseases other than HIV, the opinion of the clinicians providing the clinic was that the vast majority of appointments were likely to have been HIV related. It is also worth noting that in CUH the hepatology service provides care and treatment for hepatitis C infection, and co-infected patients attend both services separately.

Missed visits. The overall missed visit rate for scheduled infectious disease clinic appointments was 12% (158/1338); however, missed visits were concentrated in a minority of patients, as 75% of patients missed no visits, 15% missed a single visit and 10% missed two or more visits. Patients not on HAART at the time of the scheduled visit were significantly more likely (odds ratio 2.7, 95% CI 1.3–5.6) to miss their appointment.

Other outpatient specialties. Over one-third of patients ($n=120$) had at least one outpatient appointment scheduled with a specialty other than infectious diseases (454 appointments) in CUH. The most frequently scheduled non-ID outpatient appointments were obstetrics and gynaecology (48% of appointments), psychiatry (7%), gastroenterology (6%), haematology (5%), ophthalmology (5%) and orthopaedics (5%). Although use of non-ID outpatient specialities might be expected to be more frequent in older patients, the total proportion of patients ≥50 years of age with scheduled non-ID outpatient appointments (excluding obstetric and gynaecology appointments) did not differ

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Table 1. Number (days) of in-patient episodes by primary diagnosis code and HIV category.

Primary diagnosis (ICD-10 AM chapter)	Codes	HIV related	HIV associated	Unrelated to HIV
Infectious and parasitic diseases	A00–B99	7 (88)		
of which, HIV diagnoses	B20–24	*4 (35)*		
Neoplasms	C00–D48	1 (33)		
Diseases of the blood and blood-forming organs and immune mechanism	D50–D89			1 (1)
Endocrine, nutritional and metabolic diseases	E00–E90			1 (1)
Mental and behavioural disorders	F00–F99			1 (1)
Diseases of eye and adnexa	H00–H59	1 (3)		
Circulatory system diseases	I00–I99			3 (6)
Respiratory diseases	J00–J99		1 (3)	1 (1)
Digestive diseases	K00–K93			3 (18)
Diseases of the skin and subcutaneous tissue	L00–L99	2 (5)		1 (1)
Diseases of the musculoskeletal system and connective tissue	M00–M99	1 (11)		2 (2)
Genitourinary system diseases	N00–N99		1 (1)	5 (13)
Pregnancy, childbirth and puerperium	O00–O99			21 (108)
Symptoms, signs not elsewhere classified	R00–R99		2 (7)	4 (20)
Injury, poisoning and certain other consequences of external causes	S00–T98			5 (110)
Total		**12 (140)**	**4 (11)**	**48 (282)**

significantly from younger patients ($\chi^2 = 0.02$, $p = 0.88$). The missed visit rate for scheduled appointments with non-ID specialties was 17%.

Admissions

There were 64 in-patient episodes (in 48 patients) in 2012, of which 19% ($n = 12$) were categorised as HIV related and a further 6% ($n = 4$) as HIV associated. The overall in-patient admission rate was 0.2 admissions (mean length of stay 1.4 in-patient days) per patient year. Eight in-patient days (2%) were intensive care days (two patients). The primary diagnosis coded for each in-patient episode can be seen in Table 1. Of note was that 11 admissions (17%, 95% CI 9%–29%) did not have a HIV-related diagnosis code (B20–24) recorded in any of the 30 available diagnoses fields. Nearly, all of these admissions were classed as unrelated to HIV; however, one was classed as HIV associated.

There were also 198 day-case admissions (defined as planned admissions not requiring an overnight stay[15]) in 2012. The vast majority of these were incurred by two patients, one on haemodialysis (158 day-case admissions) and the second undergoing radiotherapy for a HIV-associated condition (27 day-case admissions). Of the remaining 13 day-case admissions, 4 were considered HIV related and 2 HIV associated.

ED visits

There were 99 ED visits by 60 patients (18% of patients), giving an average ED visit rate of 0.3 visits per patient year. Forty-three per cent of these visits resulted in admission, one-quarter of which were considered HIV-related admissions.

Costs

The non-drug cost to the hospital of providing care for the HIV patients included in this study in 2012 can be seen in Table 2.

As would be expected, the type of costs incurred differed by CD4 category, with patients with lower CD4 counts having a higher proportion of their costs due to HIV-related in-patient care, while those with higher CD4 counts had little HIV-related in-patient care. Most notably, the 2% of patients with a CD4 count < 50 cells/μL accounted for 50% of in-patients costs (€194,369/€390,301) and 27% (€209,725/€769,503) of the total cost of providing care for HIV patients in 2012.

The overall mean non-drug cost PPM was €210 (€122–€297). On univariate testing, patients ≥ 50 years of age were significantly less expensive than younger patients ($p < 0.0001$). This difference remained significant when all obstetric/gynaecology costs were

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Table 2. Proportion of non-drug costs by type of care, proportion of patients who used each care type ($n = 328$), and for those who used each type of care the mean, median and inter-quartile range (IQR) of non-drug costs per patient month, 2012.

	Total non-drug costs (%)	Patients incurring cost, % (95% CI[a])	Non-drug cost per patient month		
			Mean	Median	IQR
Outpatient appointments					
Infectious diseases	30	100	€63	€54	€45–€72
Other specialties	13	37 (32–42)	€69	€21	€10–€50
Outpatient subtotal	43	100	€90	€61	€47–€91
In-patient episodes					
HIV related	17	3 (2–6)	€1584	€656	€291–€1968
HIV associated	1	1 (0.2–3)	€207	€159	€146–€317
Unrelated to HIV	33	12 (9–16)	€605	€182	€75–€342
In-patient subtotal	51	15 (11–19)	€781	€210	€79–€425
Day case admissions					
HIV related	0	1 (0.2–3)	€55	€47	€18–€97
HIV associated	1	1 (0.2–3)	€258	€57	€56–€661
Unrelated to HIV	3	2 (1–5)	€228	€51	€20–€61
Day case subtotal	4	4 (2–7)	€201	€57	€24–€62
Emergency Department visit					
All ED visits	2	18 (14–23)	€27	€17	€15–€29
Total	**100**		**€210**	**€64**	**€47–€105**

[a]Agresti–Coull 95% confidence interval.

excluded. Patients who had been diagnosed late were significantly more expensive than those diagnosed early ($p = 0.01$). Costs also differed significantly by CD4 category ($p = 0.0001$), year of diagnosis ($p < 0.0001$) and HAART/suppression category ($p = 0.0001$).

On multivariate analysis of total non-drug costs, the only predictor of non-drug costs that remained significant on adjustment was CD4 < 50 call/μL (Table 3).

Discussion

This study reports the range, frequency and cost of healthcare services used by HIV patients in a single centre in the south of Ireland in a single calendar year (2012).

We have previously reported the cost of HAART for this cohort in 2012 was €856 PPM,[13] making HAART costs around 80% of the total cost of providing care in 2012 (excluding other drug costs). This is a similar proportion to what has reported previously in other countries.[17–20] Although HAART is expensive, it is a very cost-effective treatment,[21,22] and not only vastly improves individual outcomes, but also has population level benefits, reducing onward transmission.[23] In this cohort, 77% of patients were on HAART for the entire period of the study with a further 11% initiating HAART during 2012, just 7% of patients received no HAART in 2012 (their average CD4 count was 510 cells/μL). Of patients who were on HAART for more than six months, the most recent viral load result was <50 copies/mL for 90% of patients, treatment and response figures which are comparable to other developed countries.[24–26]

Unsurprisingly, outpatient infectious disease care was the most frequently used service by this group of patients, accounting for 30% of all non-drug costs in 2012 (Table 2). One-third of patients also had outpatient appointments with other specialties, and while the overall cost of non-ID outpatient appointments was 13% of total non-drug costs, within the subgroup patients using other services nearly half of their outpatient costs were due to use of non-ID services. It is well established in the literature that as patients age they are experiencing increasing levels of non-HIV morbidity,[27] rates of which are higher than in comparable HIV-negative populations.[7,28] It is a limitation of our study that we do not have information on patient co-morbidities, and can only use other services as an indicator of possible non-HIV morbidity. Hospital outpatient appointments are likely to underestimate the burden of non-HIV morbidity as infectious disease specialists may be dual trained or patients may attend other hospitals/primary care services for their non-HIV care. Conversely, patients may also be referred to other specialties for investigations that subsequently prove negative. There were relatively few patients ≥ 50 years of age in this cohort in 2012, so unfortunately it was not possible to carry out any meaningful analysis

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Table 3. Mean HIV related/associated, HIV unrelated and total non-drug costs PPM 2012, by subgroups, and significance of differences on univariate testing and multivariate (GLM inverse gaussian family, identity link) analysis.

			Mean cost PPM			
Patient subgroup		N	HIV related/associated	HIV unrelated	Total	Multivariate analysis of total non-drug costs (P)
Gender	Male	194	€121	€111	€235	Ref
	Female	134	€79	€87	€173	0.52
≥50 years	No	286	€112	€114	€231	Ref
	Yes	42	€48	€18	€68	0.14
Risk factor	MSM	96	€151	€49	€203	Ref
	COHP	133	€78	€57	€140	0.84
	Heterosexual	64	€73	€98	€177	0.51
	IDU	18	€94	€599	€701	0.51
	Other/unknown	17	€170	€275	€453	0.6
Minimum CD4 count in 2012	500+	169	€58	€38	€100	Ref
	350–499	85	€67	€79	€148	0.5
	200–350	52	€103	€197	€306	0.55
	50–199	14	€176	€143	€323	0.07
	<50	7	€1840	€1340	€3227	0.02
Late diagnosis	No	137	€75	€104	€185	Ref
	Unknown	77	€76	€195	€276	0.31
	Yes	114	€156	€36	€196	0.34
Years since diagnosis	11+ years	96	€57	€85	€145	Ref
	6–10 years	107	€69	€115	€189	0.71
	1–5 years	100	€108	€80	€194	0.69
	Diagnosed 2012	18	€918	€380	€1319	0.35
HAART & Viral load category	On HAART suppressed	211	€64	€75	€143	Ref
	On HAART not suppressed/undetermined	44	€137	€80	€217	0.49
	Started/stopped HAART	49	€293	€307	€611	0.51
	No HAART	24	€98	€37	€143	0.26

Ref: reference category; COHP: person from a country of high prevalence; MSM: men who have sex with men; IDU: injecting drug user; HAART: highly active anti-retroviral therapy.

Note: 'Late diagnosis' defined as CD4 count < 350 cells/μL or AIDS defining illness at diagnosis, 'on HAART' defined as patient on HAART for the entire duration of their time in the study, 'suppressed' defined as all viral loads in 2012 <50 copies/mL, with one viral load 50–499 copies/mL allowed if previous and following viral load tests < 50 copies/mL. Total non-drug costs PPM includes the cost of ED visits.

of their use of specific non-ID services. In contrast to what has previously been reported in the literature,[19] the cost of care for older patients in this study was lower than that for younger patients, although this was no longer significant when adjustment was made for confounding factors (Table 3). We previously reported a similar finding for the cost of HIV outpatient care alone, and postulated that this result was due to the particular characteristics of the cohort attending CUH.[13] However, this study does provide baseline data which will be useful to assess potential changing resource use with the ageing of the patient cohort.

An interesting finding was that 17% (95% CI 9%–29%) of admissions had no HIV diagnosis coded in any of the 30 available diagnoses fields. There are two possible reasons for this discrepancy, HIV diagnoses may not have been documented in the medical records available to the coders (as doctors may not have asked about, or patients may not have disclosed their HIV status), or errors may have occurred during the coding process. Previous studies examining the accuracy of diagnostic coding in Irish public hospitals have highlighted the limitations of such data for research purposes.[29–31] The benefits of clinician awareness of and involvement in the coding process have previously

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been demonstrated[30] and as healthcare funding structures in Ireland change, from block grant budgets to an activity-based 'money follows the patient' approach,[32] clinician education on the importance of clear and complete documentation as well as regular auditing of coding and detailed analysis of local data to identify possible data quality issues[33–35] are likely to become critical factors in hospital funding.

We recognise that there are several important limitations to this study. The study was carried out in a single centre which has a lower proportion of injecting drug users than the total HIV population in care in Ireland (6% vs 21% nationally); however, the study population was similar to the national HIV population in care in terms of age (mean age 40 years for both), gender (59% male CUH vs 62% male nationally) and clinical characteristics (80% on HAART nationally).[36] No information was collected on patients' use of other hospitals, while the nearest alternative HIV centre is 100 km away, there are four other hospitals in the region providing emergency care which patients could have accessed and which would not have been included in this study. The cost of appointments with allied health professionals within CUH was not included nor was any patient use of non-hospital health services (GPs, community care). It was also not possible to distinguish HIV-morbidity associated use of non-ID outpatient hospital services. As a clinical database routinely updated with viral load results was used to initially identify all patients who attended in 2012, eligible patients may have been missed if a patient attended and did not have a viral load test performed or if the viral load was not entered on the database. As the possibility of a patient who had attended in 2012 but who had no corresponding viral load result in the database would be more likely to happen if a patient only attended once in 2012, this could be a source of selection bias in this study. Probably the biggest limitation, however, is the lack of a HIV-negative comparison group, meaning it was not possible to estimate how much healthcare use in this cohort was additional to what would be normally used by similar patients without HIV infection. National surveys have reported the 12-month prevalence of use of hospital services by the general population to be 10% for emergency services, 20% for outpatient services, 9% for day patient admissions and 10% for in-patient admissions.[37,38] The overall prevalence of ED and non-ID outpatient clinic use was higher in our study (18% and 33%, respectively) as were the age-specific rates. The proportion of patients admitted following an ED episode (43%) was also higher than the reported proportion of ED episodes that result in admission overall in Ireland (25%).[39] The rates of non-HIV admissions were very similar to the rate of in-patient admission in the general population (11%), although the rate of day-case attendance appeared slightly lower than in the general population (4%).

Data on the use and cost of health service use by HIV patients are very useful for both planning of health services and for use in health technology assessments and cost-effectiveness studies. The prevalence approach to costing, as used in this study, is particularly informative for policy makers and planners as it provides a snapshot of the total cost for a particular year given the mix of patients present, whereas an incidence approach, which would be better at identifying and estimating the costs for particular types of patients, or particularly resource intensive periods of patient care (e.g. following diagnosis, approaching death, etc.) does not necessarily provide the type of information that can be easily used for planning. Information on the range and frequency of other specialties accessed by this population can also be used to inform the long-term organisation of services and co-ordination and integration of care across specialties.

While our study provides baseline information on the frequency and type of hospital services used by HIV patients, further work to estimate the costs and resource use during intensive phases of care, such as following diagnosis, or approaching death would be useful for making more accurate estimates for health technology assessments and cost-effectiveness analyses. As Ireland's healthcare financing structures are reformed, it is particularly important that the costs of complex patients, such as HIV patients, are adequately accounted for in new financing structures.

Acknowledgements

The authors thank all staff members of Cork University Hospital who participated in the micro-costing study and Andrew Murphy for provision of hospital cost data.

Authors' contributions

AB, MH and CJB were involved in the study design. AB carried out the data collection with advice from AJ, MH and CJB. AB analysed and drafted the article; all authors contributed to the interpretation of the findings and article revisions. All authors approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research was funded by the HRB in Ireland under Grant No. PHD/2007/16.

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- Brennan A, Browne JP, Horgan M. A systematic review of health service interventions to improve linkage with or retention in HIV care. AIDS Care. 2014;26(7):804-12.

AIDS Care, 2014
Vol. 26, No. 7, 804–812, http://dx.doi.org/10.1080/09540121.2013.869536

A systematic review of health service interventions to improve linkage with or retention in HIV care

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(*Received 17 January 2013; final version received 19 November 2013*)

The importance of early linkage to and continuing retention in HIV care is increasingly recognised, particularly in light of the implications poor linkage and retention rates have for the effectiveness of HIV treatment as prevention strategies. The purpose of this systematic review was to examine the effectiveness of healthcare interventions in improving patient linkage to or retention in HIV care. We systematically searched PubMed (MEDLINE and PubMed-only citations) and EMBASE databases for articles reporting the original results of randomised controlled trials, and used a standard data collection form to extract information on study characteristics and outcome data. Five articles met the inclusion criteria, of which two articles focused on linkage to care and three on retention in care. The methodological quality, both of internal and external validity, of most of the trials was suboptimal. Wide variation in the interventions and outcome measures meant synthesis of the results using meta-analysis was not appropriate. This review shows evidence that interventions based on supporting patient self-management improves linkage to, and possibly retention in, care. Interventions aimed at delivery service design may also be effective, although evidence in this review was limited. It is vital that interventions are developed to improve patient engagement in HIV care. The dearth of research identified by this review highlights the need for well-designed trials of interventions in this area in the future.

Keywords: HIV/AIDS; linkage to care; adherence to care; loss to follow-up; retention in care; review

Introduction

Early linkage to and regular attendance for human immunodeficiency virus (HIV) care are associated with improved patient outcomes (Giordano et al., 2007). Full engagement in care enables timely treatment with appropriate anti-retroviral medications, and early detection and management of medical complications. However, HIV care providers around the world report issues with poor linkage and retention of patients (Fleishman et al., 2012; Lamb, El-Sadr, Geng, & Nash, 2012; Rice, Delpech, Chadborn, & Elford, 2011). In addition, recent evidence on the decreased infectivity of those on treatment (Cohen & Gay, 2010) has generated considerable interest in the potential of HIV "treatment as prevention" strategies, but the effectiveness of these strategies are reduced considerably by poor patient engagement (E.M. Gardner, McLees, Steiner, Del Rio, & Burman, 2011; Mugavero et al., 2012).

Modern anti-retroviral treatments have changed HIV from an ultimately fatal disease in the majority of those infected to a chronic condition managed in an ambulatory care setting. People diagnosed with HIV today can have a near-normal life-expectancy (van Sighem, Gras, Reiss, Brinkman, & de Wolf, 2010), and, consequently face decades of healthcare use following diagnosis (Nakagawa et al., 2012). Managing chronic conditions is challenging for both patients and their healthcare providers. Patients require education and support to effectively manage their illness, while healthcare providers need to take a more proactive collaborative approach to providing care (Wagner, Austin, & Von-Korff, 1996). Research into chronic disease management has concentrated mainly on non-communicable chronic diseases; however, many of the problems and potential solutions apply to all chronic diseases, including HIV. The chronic care model (CCM) is the basis for many interventions (Wagner et al., 1996). The CCM identifies six interrelated components: healthcare organisation, community resources, self-management support, delivery system design, decision support and clinical information systems. To summarise briefly: the structure, goals, values and reimbursement policies of healthcare organisations should prioritise and reward chronic care; healthcare organisations should link with community-based resources (e.g., support groups); patients and their families should be given the self-management skills and tools to become their own primary care-givers; care delivery systems should be designed to support patient self-management and deliver a more proactive service; evidence-based clinical practice guidelines should be used routinely by clinicians; and computerised information

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systems should be used to facilitate routine patient reminders/appointments, to provide feedback to clinicians, and to develop patient registries for planning individual and population-level care (Bodenheimer, Wagner, & Grumbach, 2002). Chronic disease management programmes have been shown to have a positive outcome on markers of process and intermediate outcome measures; however, their effects on healthcare utilisation rates and clinical outcomes are less clear (Bodenheimer et al., 2002; Mattke, Seid, & Ma, 2007).

A systematic review of organisation of care for HIV found that case-management interventions improved mortality and anti-retroviral use, but evidence was mixed regarding other outcomes and other health service interventions (Handford, Tynan, Rackal, & Glazier, 2006). The review did not include measures of linkage or retention as outcome measures of interest. Other reviews in this area have not reviewed the outcomes of interventions specifically (Kranzer, Govindasamy, Ford, Johnston, & Lawn, 2012), have not been systematic (Mugavero, Norton, & Saag, 2011), have not included both linkage and retention (Higa, Marks, Crepaz, Liau, & Lyles, 2012) or have been limited geographically (Higa et al., 2012; Kranzer et al., 2012; Liau et al., 2013; Marks, Gardner, Craw, & Crepaz, 2010).

This paper aims to review the effectiveness of healthcare interventions to improve either patient linkage to or retention in HIV care, without geographic limitation.

Methods

Inclusion criteria

We included studies reporting original results of randomised controlled trials of healthcare interventions to improve HIV patient linkage or retention in care. Healthcare interventions were defined as "Any type of treatment, preventive care, or test that a person could take or undergo to improve health or to help with a particular problem" (Agency for Healthcare Research and Quality (n.d.)).

We excluded studies focused only on adherence to anti-retroviral therapy or subgroups of patients and articles published in a language other than English.

Outcomes of interest were: proportion of patients linked into and retained in care, proportion of appointments attended or proportion of patients lost to follow-up.

Search strategy

We systematically searched PubMed (1966–present) and EMBASE (1974–present) using the keyword search shown in Table 1. We also searched the reference lists of included articles, but searches for unpublished, grey literature and conference abstracts were not carried out.

Table 1. Keyword search strategy used to search PubMed (1966–Jul 2012) and EMBASE (1974–July 2012).

#1	outpatient OR out-patient
#2	ambulatory
#3	outpatient clinic
#4	outpatient setting
#5	outpatient care
#6	ambulatory care
#7	primary care
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	human immunodeficiency virus
#10	HIV
#11	AIDS
#12	#9 OR #10 OR#11
#13	patient compliance
#14	retention
#15	engagement
#16	linkage
#17	#13 OR #14 OR#15 OR#16
#18	randomised controlled trial
#19	#8 AND #12 AND #17 AND #18

This search retrieved 120 articles from PubMed and 55 articles from EMBASE (date of search 10/07/2012). Following removal of duplicates and non-English language articles 140 references remained. The study selection process can be seen in Figure 1.

Data extraction

One reviewer (AB) reviewed all articles and abstracted relevant data using a data collection form developed based on Cochrane guidelines (Higgins & Green, 2011). A second reviewer (JB) independently cross-checked the data extracted. Risk of bias of included studies was assessed using risk of bias tools in Review Manager 5.1 (Figure 2).

Description of studies

In total, nine studies were fully reviewed and four were excluded for the following reasons: two focused solely on patients taking anti-retroviral therapy (ART) (Kunutsor et al., 2011; Laurent et al., 2011), one examined the effect of a housing intervention (not a healthcare intervention) (Kidder et al., 2007) and one study (L.I. Gardner et al., 2009) was excluded as it reported secondary analysis of a study included in the review (L.I. Gardner et al., 2005).

Of the five studies included, two focused on linkage to care and three on retention in care or attendance rates (Table 2).

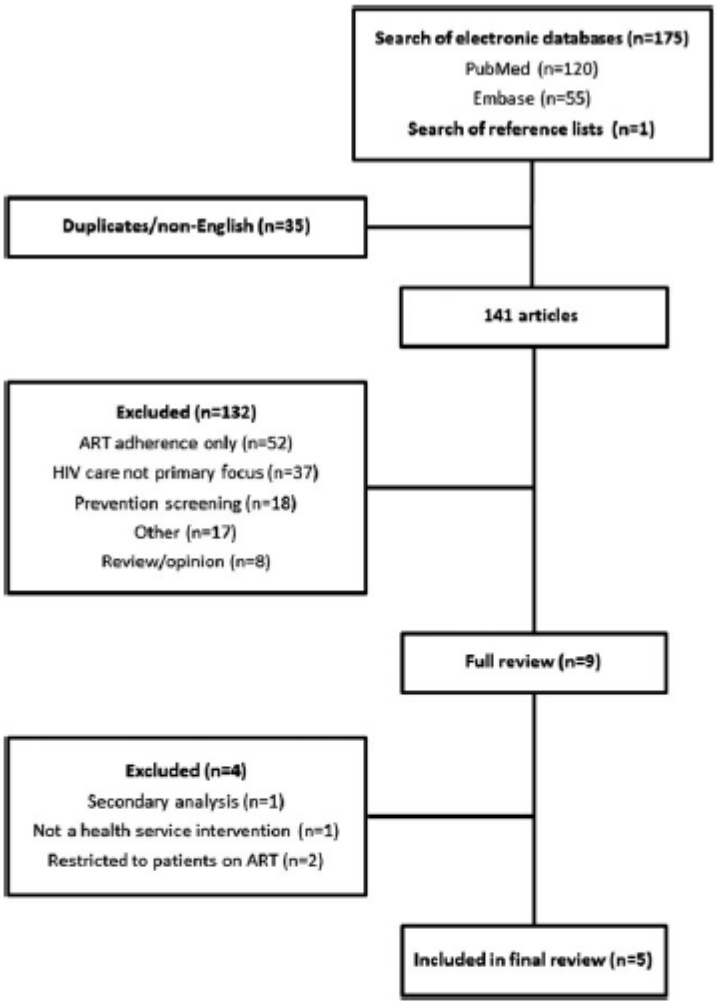


Figure 1. Flow chart of article selection.

Linkage

L.I. Gardner et al. (2005) recruited newly diagnosed patients who were not currently in care from a wide variety of sources in the USA and randomised them to receive a strengths-based case-management intervention or standard referral. In a strengths-based case-management approach the case manager works with the patient to help them identify their own internal strengths and assets, which in turn empowers patients to acquire needed resources and resolve issues for themselves (L.I. Gardner et al., 2005). Up to five case-management contacts per patient within 90 days of randomisation were allowed in the intervention arm. The primary outcome was the proportion of patients who attended a HIV care provider at least once in each of two consecutive six-month periods.

Wanyenze et al. (2011) investigated the effect of routine in-patient HIV counselling and testing (HCT) compared to referral for HCT post-discharge (standard care at the time of the study) (Wanyenze et al., 2011). Patients were recruited from a single hospital in Kampala, Uganda. The primary outcome measures were uptake of HIV testing, linkage to care including antiretroviral therapy and survival.

Retention

Three studies looked at people already linked into care (Naar-King, Outlaw, Green-Jones, Wright, & Parsons, 2009; Perron et al., 2010; Wohl et al., 2011).

A pilot study was carried out by Naar-king et al. (2009), comparing peer outreach workers to traditional mental health clinicians in delivering motivational

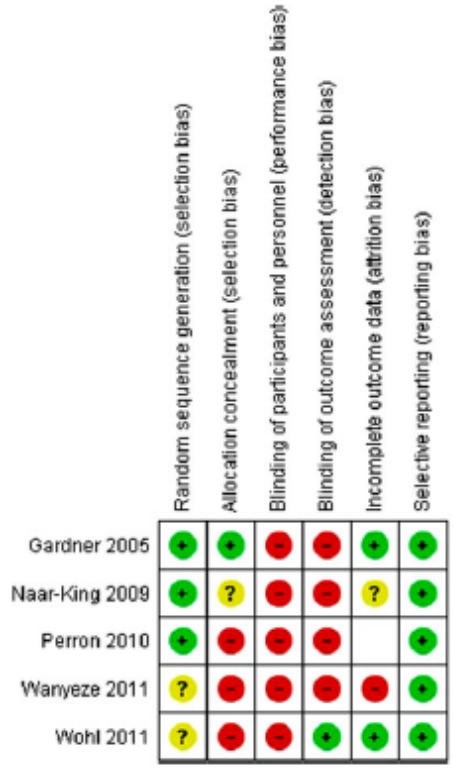


Figure 2. Risk of bias in included studies.
Note: Red circles indicate a high risk of bias, green circles indicate a low risk of bias and yellow circles indicate that risk of bias is unclear/unknown. If a bias is not relevant to a particular study no circle is displayed.

interviewing. The study's primary outcomes were treatment fidelity (i.e., competency of peer-workers to deliver the intervention) and retention in care. This study measured retention in care using a 5-point gap scale corresponding to the number of quarters in the 12 months of follow-up in which the participant did not attend for routine HIV care (i.e., 0 = attended in all four quarters, 1 = one quarter with no attendance recorded and so on).

A trial of a reminder system on missed out-patient appointment rates was carried out in Switzerland (Perron et al., 2010). There were 2123 patients included in total; however, only a subset ($n = 303$) were attending the HIV ambulatory clinic. Reminder telephone calls were made 48 hours before scheduled out-patient appointments. Up to three attempts were made to telephone patients, followed by a text message or a postal reminder (if no telephone or mobile number was available). The primary outcome was the rate of missed appointments in the clinics. Number of reported, cancelled and rebooked appointments, as well as the number and timing of contacts made, and the cost-effectiveness and acceptability of the intervention were also examined.

A bridging case-management intervention to facilitate prisoners' entry and retention in HIV care post-release was tested in the USA (Wohl et al., 2011). The intervention was based on the strengths-based model of case management. Participants were prisoners with between four weeks and three months remaining in their sentence. Case managers attempted to meet participants a minimum every two weeks prior to release, twice the first week following release, weekly for the following two weeks and then at two weekly intervals up to six months after release. The control group received discharge planning from a HIV outreach nurse who worked with inmates approximately three to six months prior to their release to make referrals to community clinics and social services, identify sources for coverage of medication expenses and attempt to locate housing. Nurses met with inmates approximately three times prior to release but did not provide any supportive services or follow-up following their release. Participants in both arms of the trial were interviewed at study entry, two weeks prior to release, and at weeks 2, 8, 24, 36 and 48 post-release. In addition, at weeks 4, 12, 16, 20, 28, 32 and 40 brief telephone interviews were performed. Primary outcome measures were self-reported access to medical care at weeks 4, 12, 24 and 48.

Results

Methodological quality of studies

There were potentially important methodological issues with all studies included in this review. Random allocation of study participants to the intervention or control group, a key feature of RCTs, is performed in order to minimise selection bias. The process of randomisation was unclear for two studies and allocation concealment (concealment of the allocation sequence from those enrolling/assigning participants) was only reported in detail by one study (Figure 2). In particular, the selection of participants by Wanyenze et al. (2011) appears to be very vulnerable to bias. There were large differences in the HIV positivity rate found in the intervention (57%) and control arms (39%); this difference could be explained by the large difference in completion of testing (99% intervention versus 69% control). The results of this trial favoured the control arm, probably due to underlying differences in the type of controls that completed the testing process.

Blinding of participants and study personnel (those who implement the intervention, measure the outcomes or analyse the data) should be carried out where possible in order to minimise differences in behaviour across

Table 2. Characteristics of included studies.

Reference	Setting	Intervention	Sample	Outcome measure	Follow-up	Notes
Linkage						
L.I. Gardner et al., 2005	Health department testing centres, STD clinics, hospitals, community-based organisations, United States (multiple sites)	Brief case management intervention vs simple referral for care	316 HIV positive patients >18 years, not engaged in care, diagnosed in previous 6 months	Self-reported attendance at HIV care provider at least once in each of 2 consecutive 6-month time periods, verified by medical record review	6 and 12 months after baseline	Inclusion criteria changed halfway through study to include people diagnosed more than 6 months previously
Wanyenze et al., 2011	Hospital, Uganda	Routine offer of HIV counselling and testing (HCT) to medical inpatients vs standard care (referral for out-patient HCT)	153 HIV positive patients (of 500 in-patients enrolled)	Self-reported attendance at HIV/AIDS clinic	3 and 6 months after baseline	
Retention						
Naar-King et al., 2009	HIV care programme within an adolescent medicine department, United States (Michigan)	Motivational interviewing (MI) by peer outreach workers vs MI by master's level staff	83 HIV positive aged 16–29, enrolled in medical care in the study centre	Gaps in attendance for primary HIV care. 4-point gap score indicating the number of quarters without a visit (i.e., 0 = at least one visits in all four quarters, 4 = no visit in any quarter), identified by medical chart review	12 months	Pilot study – powered to estimate effect size not to find significant differences
Perron et al., 2010	Ambulatory HIV clinic, Switzerland	Reminder within 48 hrs of appointment (phone call, sms, postal reminder) vs no reminder	303 patients scheduled to attend the HIV ambulatory clinic (of 2130 patients in overall study)	Proportion of missed appointments as recorded on the electronic patient appointment scheduling system		
Wohl et al., 2011	Prison inmates, United States (North Carolina)	Bridging case management vs standard referral	89 HIV positive inmates, > 18 years, between 4 weeks and 3 months left in their sentence	Self-reported attendance for routine medical care	4, 12, 24, 48 weeks after release	

groups. It is generally difficult to blind participants and study personnel in trials of health service interventions; however, the assessment of outcome is more amenable to blinding and should be carried out whenever possible to minimise detection bias. Blinding of outcome assessors was reported by just one study (Wohl et al., 2011).

One of the trials reported power calculations and was sufficiently powered (L.I. Gardner et al., 2005). Power calculations were not reported at all for three studies (Naar-King et al., 2009; Wanyenze et al., 2011; Wohl et al., 2011), and HIV patients were a subgroup in one trial which was not powered for subgroup analysis (Perron et al., 2010).

Study results

Linkage

Participants who received the brief case-management intervention developed by L.I. Gardner et al. (2005) were significantly more likely to have attended care at least once in each of the two consecutive six-month periods of follow-up (relative risk 1.41 95% confidence intervals 1.1–1.6).

The trial of in-hospital HIV counselling and testing versus post-discharge referral by Wanyenze et al. (2011) resulted in a significantly greater proportion of patients in the control arm reporting having attended a HIV clinic in the six-month follow-up period compared to the intervention arm (74% versus 56%). However, as previously discussed, there were large differences in the proportions completing HIV testing and diagnosed with HIV between the two groups, as well as differences in mortality between trial arms.

Retention

No significant differences were found between peer- and clinician-delivered motivational interviewing on the number of gaps in attendance (Naar-King et al., 2009). Mean pre- and post-intervention gap scores were compared for a subset of participants ($n = 37$); mean scores dropped in both groups, from 2.53 to 1.52 in the peer-worker group and from 2.76 to 1.33 in the clinician group. The authors of this paper acknowledged that this study was not powered to find significant differences, but to estimate effect sizes for future trials.

The telephone reminder intervention by Perron et al. (2010) significantly reduced the overall proportion of missed appointments from 11.4% to 7.8%; however, this intervention looked at both a primary care and a HIV clinic. On subgroup analysis the reduction in the HIV group specifically (from 15% to 12.7%) was not significant. This study also looked at the acceptability of this reminder system to patients and included an economic evaluation of the intervention. This study concluded that the intervention was effective, acceptable and economically efficient.

The study by Wohl et al. (2011), investigating the effect of an intensive case-management intervention for released prisoners, found no difference between the proportion of participants in both groups attending for HIV care at 4, 12, 24 or 48 weeks, and no difference in median time to first visit or number of visits for HIV care. However, the frequency of follow-up of both groups may have encouraged controls to attend HIV care.

As the interventions and outcome measures used by the studies included in this review were so varied, it was not appropriate to carry out any further analysis of their results.

Discussion

This systematic review identified five randomised controlled trials which looked at either linkage to or retention in HIV care. The interventions varied widely, and there were concerns about the methodological quality of most the studies identified. The outcome measures also varied, making comparisons difficult, as definitions of linkage and retention are known to affect rates detected (Mugavero, Davila, Nevin, & Giordano, 2010; Yehia et al., 2012). In addition, the method of data collection (self-reported utilisation versus documented utilisation) may also influence results obtained, as self-reported utilisation may be subject to bias (either recall or social desirability). Overall, however, these studies do provide some evidence for interventions which may be effective.

Three of the studies included in this review aimed to improve self-management support (L.I. Gardner et al., 2005; Naar-King et al., 2009; Wohl et al., 2011). The results were promising; the study by L.I. Gardner et al. (2005) in particular provides good evidence that a brief case-management intervention can substantially improve linkage to care. An observational effectiveness study subsequently carried out to examine the implementation of this intervention in a real-world setting supported the findings of the original study (Craw et al., 2008), and has also been shown to have a stronger effect in groups of patients with an unmet need or barrier, such as low education status or unstable housing (L.I. Gardner et al., 2009).

Two interventions, use of appointment reminders (Perron et al., 2010) and in-hospital HIV testing of in-patients (Wanyenze et al., 2011), were aimed at delivery system design. While little can be concluded definitively from these studies, the use of telephone reminders by

Perron et al. (2010) showed potential for reducing missed appointments, and high rates of appointment non-adherence have been shown to predict subsequent attrition from care (S. Coleman et al., 2007).

No studies were identified that targeted any of the other elements of the CCM: healthcare organisation, community resources, decision support and clinical information systems. There are many examples in the literature of initiatives targeting these components of the CCM (Korthuis et al., 2011; Magnus et al., 2012; Meulbroek et al., 2013; Oluoch et al., 2012; Woods, Samples, Melchiono, & Harris, 2003), which appear to have promising results; however, only studies included in this review were limited to RCTs. Interventions aimed at improving chronic care tend to be complex, multi-faceted and context specific and as a result evaluation by RCT is often difficult and sometimes completely unfeasible. Despite the methodological challenges, rigorous evaluations of these types of interventions are possible (Villagra & Ahmed, 2004; Wells et al., 2000).

When designing interventions in the future, researchers should be cognisant of the existing literature, not only regarding what is known about the characteristics of the effective HIV interventions already identified in this review but also of successful chronic care interventions in general (K. Coleman, Mattke, Perrault, & Wagner, 2009). In addition, effective implementation of existing interventions may be as beneficial as, if not more beneficial than, creation of new interventions (Woolf, 2008). HIV research should be looking at to the emerging discipline of implementation science to learn how best to integrate HIV research, policy and practice (Glasgow, Eckstein, & Elzarrad, 2013).

There are several limitations to this review. The literature search was not exhaustive: only two databases were searched, no unpublished or grey literature was included and articles were limited to those published in English. Considering the number of articles published on HIV, relatively few were returned by the search carried out. It is possible that important search terms were omitted.

In conclusion, given what is known about the positive effect full engagement in HIV care has on patient outcomes and the detrimental effect poor linkage and retention rates have on the efficacy of treatment as prevention strategies, it is vital that patient engagement in care is maximised. Rigorous evaluations of existing patient engagement interventions are needed, preferably using randomised controlled trials, while the features of effective chronic care interventions, such as the importance of engaging both patients and healthcare providers, should be considered during the design of any new interventions.

Acknowledgements

Contributions: AB devised, planned and carried out the systematic review and wrote the initial draft of this article; all authors contributed to the interpretation of the findings and article revisions. All authors approved the final version of the manuscript.

Funding

This work was funded by the Health Research Board in Ireland [Grant No. PHD/2007/16].

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Poster presentations:

- Brennan A, Horgan M. Repeated attendance at STI clinics in Cork and Kerry for acute STIs, a retrospective analysis 1999-2011. Poster presented at IDSI 5th Annual Scientific Meeting, Dublin, 29-29 June 2012.
- Brennan A, Horgan M. A retrospective analysis of sexually transmitted infections in older adults attending STI clinics in Cork and Kerry, 1998-2011. Poster presented at IDSI 5th Annual Scientific Meeting, Dublin, 28-29 June 2012.
- Brennan A, Jackson A, Horgan M. Modelling staff resource use in ambulatory HIV care. Poster presented at College of Medicine and Health Research Day, UCC 13 June 2013.
- Brennan A, Jackson A, Horgan M. Modelling staff resource use in ambulatory HIV care. Poster presented at ISPOR 16th Annual European Congress, Dublin, Nov 2-6 2013.
- Brennan A, Jackson A, Browne JP, Bergin CJ, Horgan M. Use of hospital services by HIV patients, 2012. Poster presented at IDSI 7th Annual Scientific Meeting, Cork, Apr 24-26 2014
- Brennan A, Jackson A, Murphy L, Horgan M. Retention in HIV care: comparison of measures and associated factors. Poster presented at IDSI 7th Annual Scientific Meeting, Cork, Apr 24-26 2014
- Brennan A, Jackson A, Browne JP, Bergin CJ, Horgan M. Use of hospital services by HIV patients, 2012. Poster presented at ISPOR 17th Annual European Congress, Amsterdam, Nov 10-12 2014
- Brennan A, Jackson A, Horgan M, Bergin CJ, Browne JP. Resource utilisation and cost of ambulatory HIV care in a regional HIV centre in Ireland: a micro-costing study. Poster presented at the SPHeRE Network 1st Annual Conference, Dublin, 9 Jan 2015.

Appendix 2. Search strategy used in "Determinants of HIV outpatient utilisation: a systematic review"

Example of search strategy and results returned (date of search 01/03/2013)

#	Terms entered	Search carried out	PubMed
1	health service	health services[MeSH Terms] OR ("health"[All Fields] AND "services"[All Fields]) OR "health services"[All Fields] OR ("health"[All Fields] AND "service"[All Fields]) OR "health service"[All Fields]	1681245
2	healthcare OR health care	("delivery of health care"[MeSH Terms] OR ("delivery"[All Fields] AND "health"[All Fields] AND "care"[All Fields]) OR "delivery of health care"[All Fields] OR "healthcare"[All Fields]) OR ("delivery of health care"[MeSH Terms] OR ("delivery"[All Fields] AND "health"[All Fields] AND "care"[All Fields]) OR "delivery of health care"[All Fields] OR ("health"[All Fields] AND "care"[All Fields]) OR "health care"[All Fields])	1231106
3	ambulatory care	ambulatory care[MeSH Terms] OR ("ambulatory"[All Fields] AND "care"[All Fields]) OR "ambulatory care"[All Fields]	70443
4	hospital	hospitals[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields]	2649336
5	outpatient OR out-patient	("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) OR ("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR ("out"[All Fields] AND "patient"[All Fields]) OR "out patient"[All Fields])	219819
6	**1 OR 2 OR 3 OR 4 OR 5**		**4431632**
7	utilisation OR utilization	utilisation[All Fields] OR ("utilization"[Subheading] OR "utilization"[All Fields])	247645
8	Cost	economics[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]	540569
9	Expenditure	health expenditures[MeSH Terms] OR ("health"[All Fields] AND "expenditures"[All Fields]) OR "health expenditures"[All Fields] OR "expenditure"[All Fields]	42637
10	**7 OR 8 OR 9**		**765770**

11	Human immunodeficiency virus OR HIV OR AIDS	(("hiv"[MeSH Terms] OR "hiv"[All Fields] OR ("human"[All Fields] AND "immunodeficiency"[All Fields] AND "virus"[All Fields]) OR "human immunodeficiency virus"[All Fields]) OR ("hiv"[MeSH Terms] OR "hiv"[All Fields])) OR ("acquired immunodeficiency syndrome"[MeSH Terms] OR ("acquired"[All Fields] AND "immunodeficiency"[All Fields] AND "syndrome"[All Fields]) OR "acquired immunodeficiency syndrome"[All Fields] OR "aids"[All Fields])	342385
12	Patient characteristics	("patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields]) AND characteristics[All Fields]	215275
13	Determinants	determinants[All Fields]	98474
14	Predictors	predictors[All Fields]	112007
15	**12 OR 13 OR 14**		**408350**
16	**6 AND 10 AND 11 AND 15**		**1299**

Appendix 3. Local clinical guidelines, CUH 2012

ROUTINE INVESTIGATION AND MONITORING FOR HIV+ PATIENTS

INITIAL DIAGNOSIS

1. **COMPLETE MEDICAL HISTORY**

2. **PHYSICAL EXAMINATION** *(including BMI and weight)*

3. **LABORATORY TESTS**
   - ✓ (Confirmatory HIV test if diagnosed outside area)
   - ✓ $CD4^+$cell count
   - ✓ HIV-1 plasma viral load
   - ✓ HIV drug resistance test (2 bottles, same VL form)
   - ✓ FBC
   - ✓ Bioprofile (LFTs, U&E)
   - ✓ Urinalysis
   - ✓ Lipid profile and glucose
   - ✓ Syphilis total antibodies and RPR
   - ✓ Toxoplasmosis IgG
   - ✓ Hepatitis B and C serology (if co-infected check HBV and HCV viral load)
   - ✓ Cervical smear test (to be organized with GP)
   - ✓ STI screening (to be organized by specialist nurse)
   - ✓ Mantoux (if CD4+cell count >200 cells/ml)
   - ✓ CXR

Note: All patients should have a GP

4. **IMMUNISATIONS**
   - ✓ Pneumococcal vaccine (if CD4+cell count >200 cells/ml)
   - ✓ Hepatitis B vaccine when sero-status is available (if CD4+cell count >200 cells/ml)
   - ✓ Influenza vaccine-yearly (from late October onwards, regardless of the CD4+cell count)

5. **CLINICAL NURSE SPECIALIST FOR EDUCATION ISSUES**
   - ✓ Safer sex, partner, status disclosed
   - ✓ GP contact/disclosure
   - ✓ Contact Tracing
   - ✓ Family planning
   - ✓ Referral to community welfare services and Group support
   - ✓ Liaison with asylum seeker screening program (Liz)
   - ✓ Advice on management of illness/side effects
   - ✓ Referral to other services as needed
   - ✓ Diet, water safety, travel, employment, Pet Contact

6. **FOLLOW-UP AFTER 4 WEEKS**

EM 30/05/2012

FOLLOW-UP VISIT

1. ON ANTIRETROVIRAL THERAPY

Monitor 2 weeks after commencing therapy:

- FBC, U&E and LFTs'
- Side effects, tolerability
- Adherence

Then monthly until fully suppressed:

- CD4+cell count
- HIV viral load
- FBC, Bioprofile
- Liaise with pharmacy in CUH
- Therapeutic modifications to be discussed with Consultant/SpR

Monitor every 3-4 months thereafter as above

2. NOT ON ANTIRETROVIRAL THERAPY

Monitor every 3-4 months

- HIV viral load (every 6 months)
- CD4+cell count
- FBC, Bioprofile
- See Clinical Nurse Specialist (particularly re family planning)
- Starting of HAART to discussed with Consultant/SpR
- Before starting HAART:
  - Adherence evaluation (motivation, social situation)
  - Medication history (OTC), recreational drugs and alcohol
  - HLA B*5701 if considering abacavir

❖ ONCE A YEAR

- Syphilis total antibodies (RPR if needed)
- Hepatitis B and Hepatitis C serology
- Cervical smear (yearly)- http://www.cervicalcheck.ie/
- Nurse Specialist Clinic: fasting cholesterol, random glucose, family planning, sexual health, drug interactions, smoking cessation advice, smear advice, vaccine review, adherence counselling, urinalysis, ECG

EM 30/05/2012

Appendix 4. Distribution of number of routine tests per patient 2012 (patients in care for 12 months, n=287)

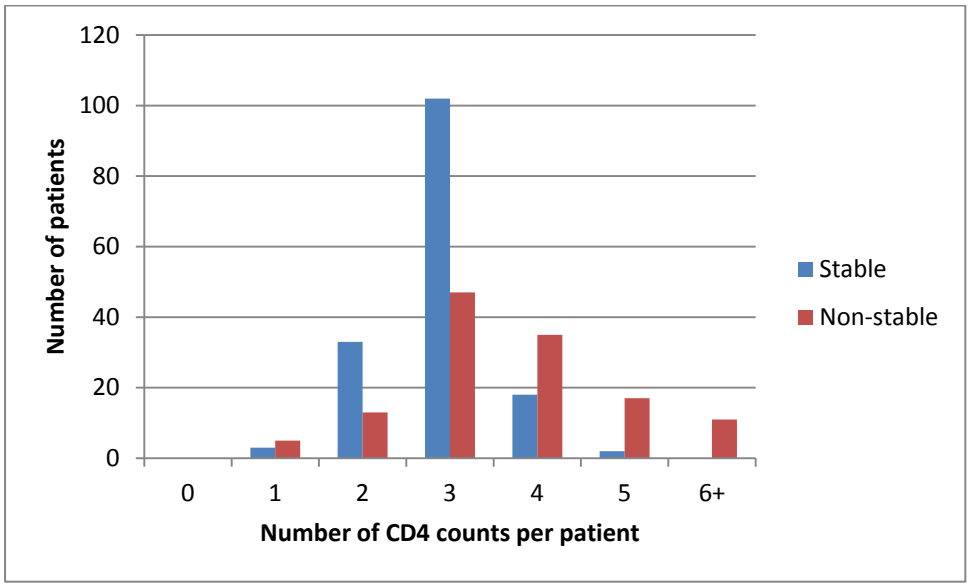


Figure A. Number of CD4 counts performed per patient in 2012, by patient type (n=287)

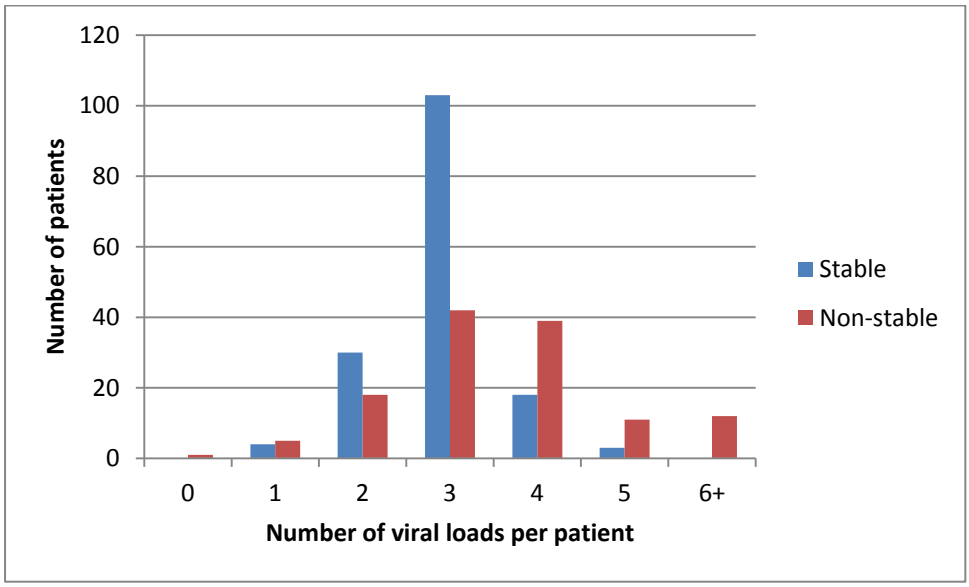


Figure B. Number of viral load tests performed per patient in 2012, by patient type (n=287)

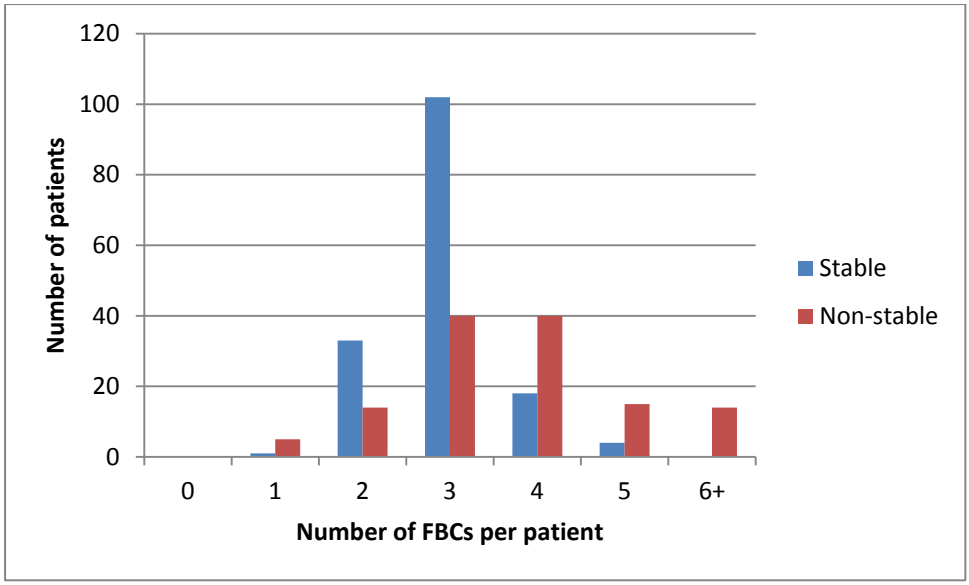


Figure C. Number of FBCs performed per patient in 2012, by patient type (n=287)

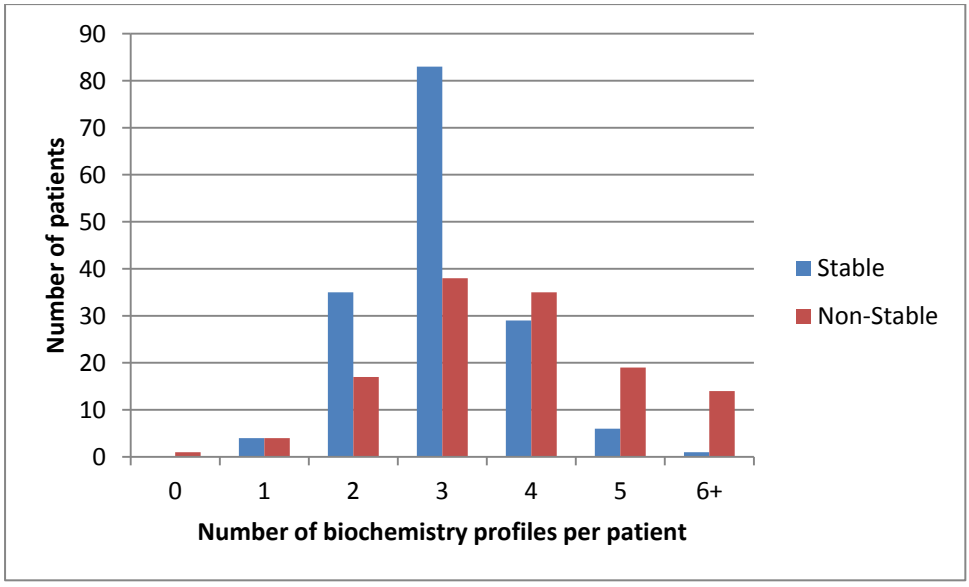


Figure D. Number of biochemistry profiles* performed per patient in 2012, by patient type (n=287)

* Includes “patient”, “ward”, “bone”, “renal/bone”, “patient & lipid”, “patient & lipoprotein”, “urea, electrolytes & creatinine” and “liver function tests”

Appendix 5. International guidelines for laboratory monitoring of (stable) patients on HAART

Test	WHO [40,302]	EACS [41]	BHIVA [75]	US (DHHS) [3]
CD4	6 months-can consider stopping CD4 monitoring	CD4 >350 12 months	3-6 months	< 2 years ART 3-6 months; >2 years suppressed CD4 300-500 12 months; > 2 years suppressed CD4>500 optional
VL	12 months	3-6 months	3-6 months	3-4 months, > 2 years suppressed 6 months
FBC		3-12 months	12 months	3-6 months (CBC with differential)
Bone profile [iv)]		6-12 months	3-6 months	
Renal				
Creatinine	at follow up if on tenofovir		3-6 months	3-6 months
Urine protein/creatinine ratio			12 months	
eGFR		3-12 months[i]	3-6 months	3-6 months
Urinalysis/urine dipstick analysis	at follow-up	12 months[ii]	12 months; if on tenofovir 3-6 months	12 months; if on tenofovir 6 months[iii]
LFTs		3-12 months	3-6 months	3-6 months
Fasting glucose[v]		12 months	3-6 months	if previous test abnormal 3-6 months; if previous test normal 12 months
Lipid profile[vi]		12 months	6-12 months	if previous test abnormal 6 months; if previous test normal 12 months

Test	WHO [40,302]	EACS [41]	BHIVA [75]	US (DHHS) [3]
Syphilis serology		12 months	MSM 3-6 months; Others 12 months	
Sexual health screen		12 months	12 months	
Cervical cytology		1-3 years	12 months	
Basic chemistry (Serum sodium, potassium, HCO3, Cl, BUN, creatinine, glucose)				3-6 months
Other recommended tests		hepatitis B & C depending on serology 12 months; Mammography 1-3 years; Rectal exam and anoscopy (MSM) 1-3 years; ultrasound and alphafetoprotein 6 months;	hepatitis B & C if indicated annually;	hepatitis B & C if indicated

i) More frequent monitoring if eGFR < 90mL/min, CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs

ii) Every 6 months if eGFR < 60 mL/min, if proteinuria ≥ 1+ and/or eGFR < 60 mL/min perform UP/C or UA/C

iii) More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

iv) Assessment of fracture risk (FRAX score) recommended also in pre-HAART and HAART patients. BHIVA recommend screening of all patients ≥ 50 years of age every 3 years, while EASC recommend screening of patients >40 years of age every 2 years

v) BHIVA guidelines do not specify glucose test to be fasting glucose. DHHS specifies either fasting glucose or HbA1C

vi) vi) DHHS specify fasting lipids

Appendix 6. Ethical approval letters

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (h) 04/09/12

20th November 2012

Professor Mary Horgan
Consultant in Infectious Diseases
Cork University Hospital
Wilton
Cork

Re: The impact of changing patient and healthcare related factors on the cost of HIV care in Ireland.

Dear Professor Horgan

Expedited approval is granted to carry out the above study at:

- Cork University Hospital
- Mid-Western Regional Hospital.

Please note that the other hospitals listed do not come under the remit of the Cork Clinical Research Ethics Committee of the Cork Teaching Hospitals.

The following documents have been approved:

- Application Form
- Study Protocol Version 1 dated 30th July 2012
- Patient Information Sheet and Consent Form Version 1 dated 7th November 2012
- Data Collection Sheet.

The co-investigator involved in this study will be:

- Ms Aline Brennan.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 3 (v) 06/05/14

4th April 2014

Professor Mary Horgan
Consultant in Infectious Diseases
Cork University Hospital
Wilton
Cork

Re: The impact of changing patient and healthcare related factors on the cost of HIV care in Ireland.

Dear Professor Horgan

The Chairman approved the following:

- Amendment Application Form
- Additional Data Collection
- Data Collection Sheet Version 1 dated 1st April 2014.

Yours sincerely

Professor Michael G Mollo
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Prof. Mary Horgan
Dr. Arthur Jackson
22 APR 2014

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Beaumont Hospital
Ethics (Medical Research) Committee

Chairperson: Professor Gerry McElvaney
Convenor: Dr. Peter Branagan

Administrator: Gillian Vale

11th December 2014

REC reference: 14/Oth/43

Ms. Aline Brennan
HRB PhD Scholar in Health Services Research
Dept of Epidemiology and Public Health
Fourth Floor Western Gateway Building
University College Cork, Cork City

Dear Ms. Brennan

14/Oth/43 – Ms. Aline Brennan (UCC) – The impact of changing patient and healthcare related factors on the cost of HIV care in Ireland

Further to email correspondence dated 26th and 27th November 2014, and your request to meet with one Beaumont Hospital (BH) staff member with a view to going through the results a Cork University Hospital (CUH) costing study and identifying differences in service provision between BH and CUH, the staff member in question to complete a short survey on BH HIV clinics / staffing levels.

I note that the purpose of the requested interaction is to *'validate the results'* of a costing study, and there is no intention to repeat the original study in Beaumont Hospital. I further note that *"no individual level data will be collected on staff or patients..., and all information provided will be treated in the strictest of confidence."*

I confirm that Beaumont Hospital Ethics (Medical Research) Committee has no objection to you contacting / meeting with / surveying a staff member using the following documents: -

1. Letter from Prof. Mary Horgan, 00/00/2014
2. Survey of HIV Centres, Version 1.1, 26/11/14

It will be a matter of personal choice / availability whether the staff member who receives the above correspondence chooses to assist in this validation.

Kind Regards

Dr. Peter Branagan
Convenor
Ethics (Medical Research) Committee

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Merlin Park University Hospital
Ospidéal na h-Ollscoile, Páirc Mheirlinne
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Block B
Main Administration Building
Merlin Park Hospital
Galway.

30th January, 2015.

Ms. Aline Brennan
Department of Epidemiology and Public Health UCC
Western Gateway Building
Western Road
Cork.

Ref: C.A. 1204 – "The impact of changing patient and healthcare factors on the cost of HIV care"

Dear Ms. Brennan,

I have considered the above project, and I am happy to grant Chairman's approval to proceed.

Yours sincerely,

pp. Colette Collins

Dr. Shaun T. O'Keeffe
Chairman Clinical Research Ethics Committee.

c.c. Dr. Catherine Fleming, Consultant in Infectious Diseases, Department of Infectious Diseases, University College Hospital, Galway.

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Aline Brennan
University College Cork
Department of Epidemiology and Public Health
UCC Western Gateway Building
Western Road
Cork

9th March 2015

RE: The impact of changing patient and healthcare related factors on the cost of HIV care in Ireland

REC Reference: 2015-03 Chairman's Action (10)
Please quote REC reference on all correspondence

Dear Ms. Brennan,

Thank you for your correspondence to SJH/AMNCH Research Ethics Committee in which you requested ethical approval for the above study.

The Chairman, on behalf of the SJH/AMNCH Research Ethics Committee has given ethical approval to this study.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

NSV Code: WPA 00406

Ospidéil OL
UL Hospitals

Ospidéal na hOllscoile, Luimneach
University Hospital Limerick

Quality & Patient Safety Department,
University Hospital Limerick
Dooradoyle
Limerick.

Tel: 061 482519
Fax: 061 482920

15th April, 2015.

Ms. Aline Brennan,
Department of Epidemiology and Public Health,
University College Cork,
Western Gateway Building,
Western Rd.,
Cork.

Re: Protocol Title
The impact of changing patient and healthcare related factors on the cost of HIV care in Ireland.

Dear Ms. Brennan,

I am in receipt of your proposal as above submitted for review by our Research Ethics Committee. I have reviewed the contents of same.

I wish to advise that I have given your study Chairperson ethical approval.

You should note that your study cannot commence until you also receive AON approval which will issue from the Quality and Patient Safety Department shortly. You are obliged to inform us as soon as your study is completed or if it terminates early for any reason.

I wish you every success with your study

Yours sincerely,

Pat Dillon,
Consultant Anaesthetist,
Chairperson, Research Ethics Committee.

ULH
Caring, Courteous and Professional

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Ospidéil OL
UL Hospitals

Ospidéal na hOllscoile, Luimneach
University Hospital Limerick

Quality & Patient Safety Department,
University Hospital Limerick
Dooradoyle
Limerick.

Tel: 061 482519
Fax: 061 482920

8th May, 2015.

Ms. Aline Brennan,
Department of Epidemiology & Public Health,
University College Cork,
Western Gateway Building,
Western Rd.,
Cork.

Re/ **Protocol Title**
The impact of changing patient and healthcare related factors on the cost of HIV care in Ireland.

Dear Ms. Brennan,

The Research Ethics Committee at the University Hospital Limerick has received a submission for ethical approval for the above study.

The following documents were reviewed and approved by the Research Ethics Committee:

Application to the Research Ethics Committee	**Approved**
Letter of Introduction	**Approved**
Study Proposal	**Approved**
Survey of HIV Centres	**Approved**

From an insurance perspective, please note that cover does not extend to those parties not employed by the Health Service Executive (HSE), or non-HSE Institutions.

Yours sincerely,

Brian McKeon,
Planning, Performance & Business Information Manager.
(For and on behalf of the Research Ethics Committee & the QPS Department).

Mater Misericordiae University Hospital
Sisters of Mercy
Eccles Street, Dublin 7, Ireland

Ospidéal Ollscoile Mater Misericordiae
Siúracha na Trócaire
Sráid Eccles, Baile Átha Cliath 7, Éire

Tel: +353 1 8032000 Fax: +353 1 8032404 Email: mmh@mater.ie Web: www.mater.ie

Not for prescription purposes

Dr Patrick W. G. Mallon
Lecturer in Medicine and
Consultant Infectious Diseases Physician
Catherine McAuley Education and Research Centre
Mater Misericordiae University Hospital
Nelson Street
Dublin 7

29th April 2015 Our Ref: 1/378/1700

RE: The impact of changing patient and healthcare related factors on the cost of HIV care in Ireland
Proposal, Version 1, 30/07/2012
Letter of Introduction, 00/00/2014
Information Leaflet, V1 07/11/2012
Information Leaflet, V 1
Consent Form, V1
Data Collection Tool V1, 07/11/2012
Survey of HIV centres, Questionnaire Version 1 16/12/2014

Dear Dr Mallon

I acknowledge receipt of your correspondence dated 27th April 2015 clarifying that the Mater Misericordiae University Hospital Pharmacy Department will not be required to provide commercially sensitive data for this research study and enclosing a Consent Form as requested by the Mater Misericordiae University Hospital and Mater Private Hospital Research Ethics Committee for the above research study to be carried out at the Mater Misericordiae University Hospital (MMUH).

This correspondence has been noted. Approval to proceed with this research study at the MMUH is granted; this approval is valid until 22nd April 2017.

It is your responsibility to adhere to the approved study protocol and ensure that all investigators involved with the research only use the approved documents without deviation (unless they have been approved by the Research Ethics Committee), to submit annual reports setting out the progress of the research (giving details of the number of participants who have been recruited, the number who have completed the study and details of any adverse events etc.) and to notify the Research Ethics Committee when the research is concluded.

The Mater Misericordiae University Hospital and Mater Private Hospital Research Ethics Committee would like to remind all investigators involved in research of their legal obligations under the law on Data Protection.

Yours sincerely

Prof Malcolm Kell
Chairman
Research Ethics Committee

c.c. Ms Aline Brennan, PhD Student, Department of Epidemiology and Public Health, University College Cork
Mr Alan Macken, Data Manager, HIV Molecular Research Group, MMUH

Directors: Mr. Thomas Lynch (Chairman), Sr. Margherita Rock, Prof. Tim Lynch, Prof. Brendan Kinsley, Ms. Mary Day, Sr. Eugene Nolan, Ms. Caroline Pigott, Mrs. Tanya King, Dr. Mary Carmel Burke, Mr. Eddie Shaw, Mr. Kevin O'Malley, Professor Desmond Fitzgerald

Registered in Ireland No. 351402 **Charity No.** CHY203 **Registered Office:** Eccles Street, Dublin 7

HEALTH SERVICES NATIONAL PARTNERSHIP FORUM

P0003 - Feb 15

Appendix 7. Survey

Version 1.1 26/11/2012

Survey of HIV centres

1) Name of centre:_____

2) Total number of patients who attended public HIV clinics in 2012_____

3) Please estimate the number of whole time equivalent (WTE) staff members in the core team of people providing outpatient HIV care in this centre in 2012:

Staff type/grade	Number of WTE in outpatient HIV service
Staff nurse (RGN)	
Clinical Nurse Specialist (CNS)	
Advanced Nurse Practitioner (ANP)	
Other nursing staff, please specify type/grade 1) 2) 3)	
Consultants	
Specialist Registrars	
SHOs	
Other NCHDs, please specify type/grade 1) 2) 3)	
Pharmacists	
Senior pharmacists	
Pharmaceutical technicians	
Senior pharmaceutical technicians	
Other staff, please specify type/grade 1) 2) 3)	

4) Which of the following types of clinics were provided for HIV patients in 2012 (please circle)?

a) General HIV-clinic Yes/No

b) Antenatal HIV clinic Yes/No

c) Vaccination clinic Yes/No

d) Co-infection clinic Yes/No

e) Others (please specify):_____
_____
_____
_____

1

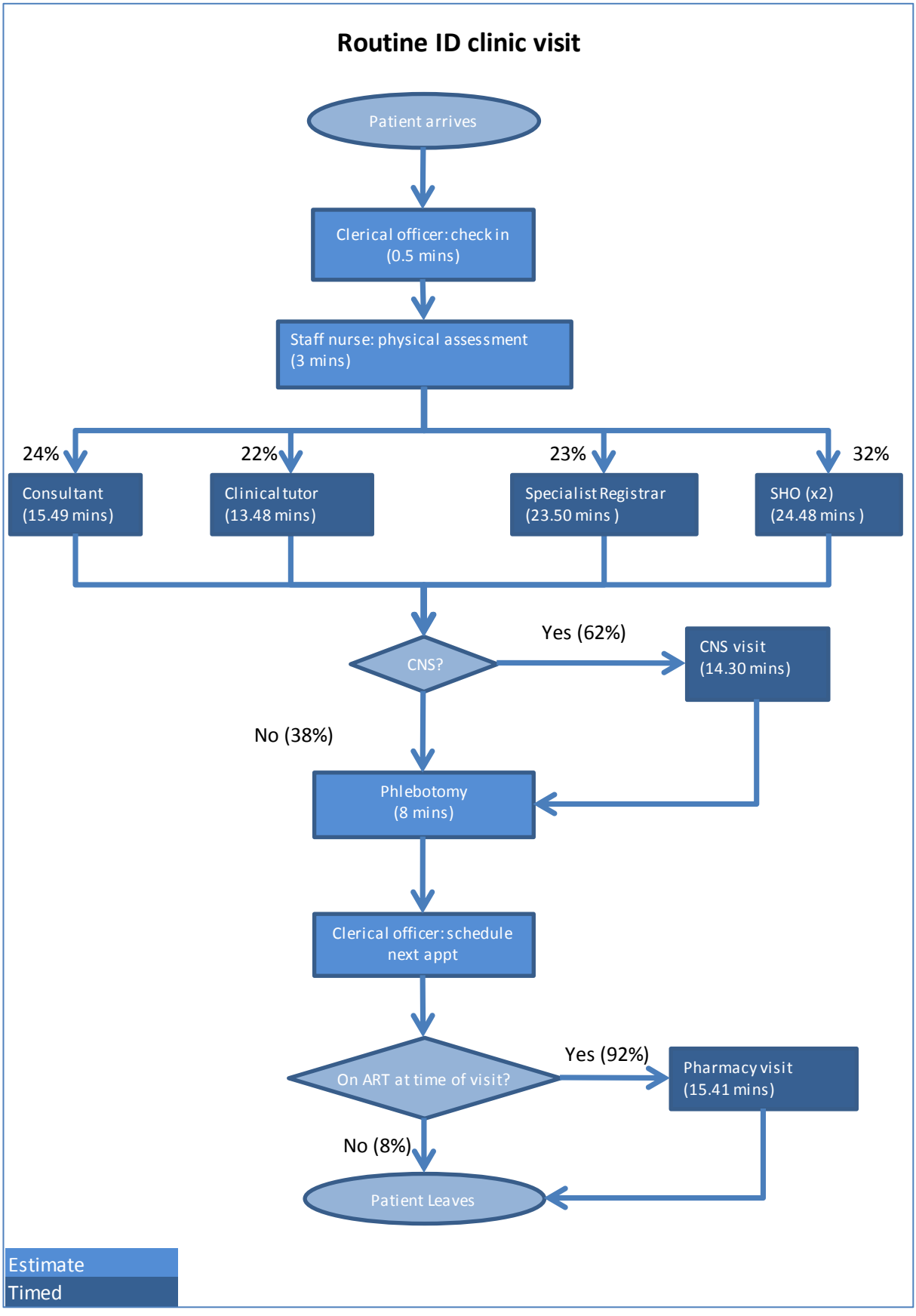
5) For each of the types of clinics held as specified above, please provide the following details (as of 2012):

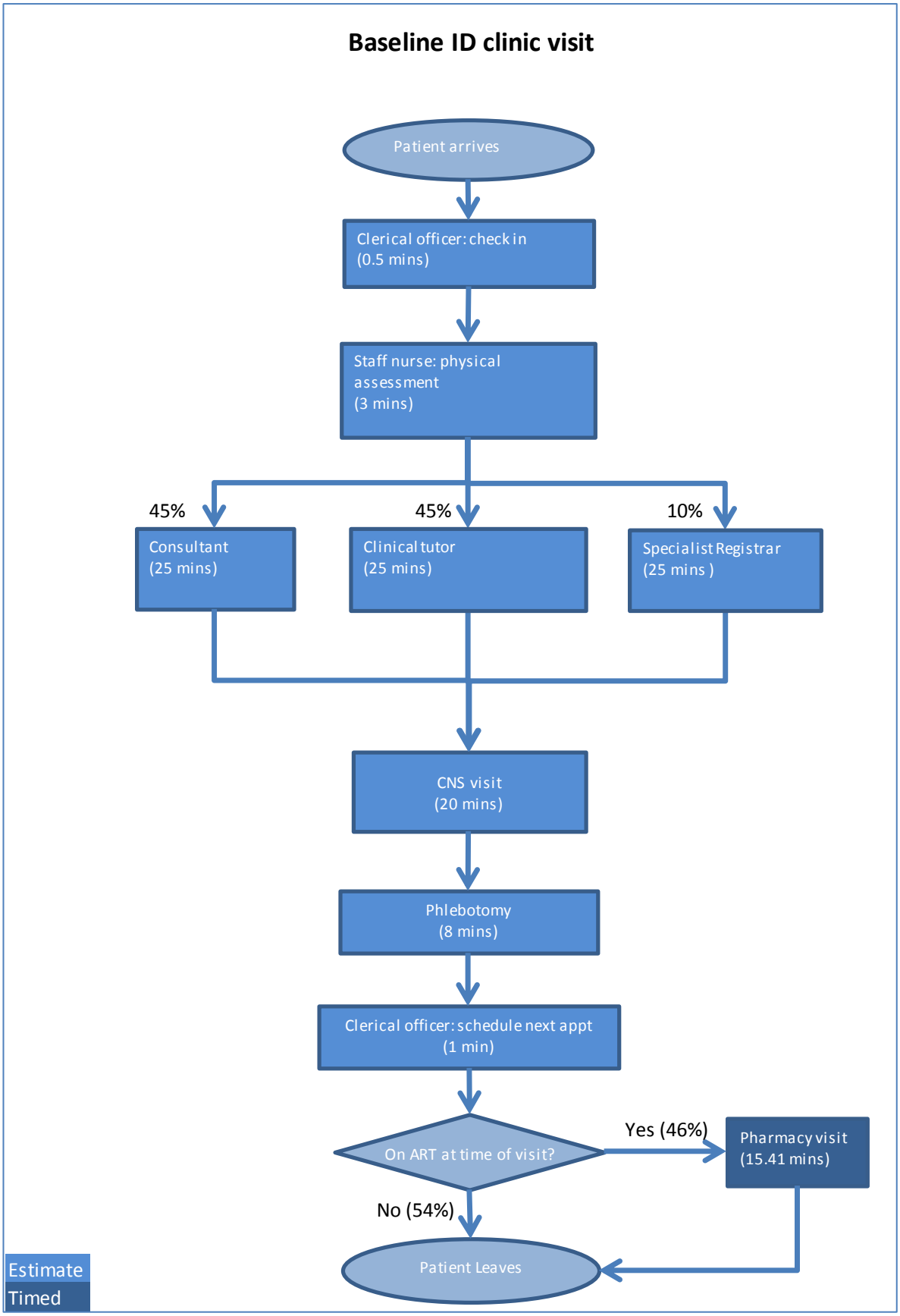
Clinic Type	HIV-clinic	Antenatal HIV clinic	HIV vaccination clinic	Co-infection clinic	Other (specify)	Other (specify)	Other (specify)
Clinic frequency (number per week/month)							
Average number of patients attending per clinic							
Proportion of patients attending which are NOT HIV positive							
Please provide the usual number of the following staff working at each clinic							
RGN							
CNS							
ANP							
Other nursing staff (please specify grades)							
Consultant							
Specialist Registrar							
SHO							
Other NCHDs (please specify grades)							
Pharmacists							
Senior pharmacists							
Pharmaceutical technicians							
Senior pharmaceutical technicians							
Other staff (please specify grades)							

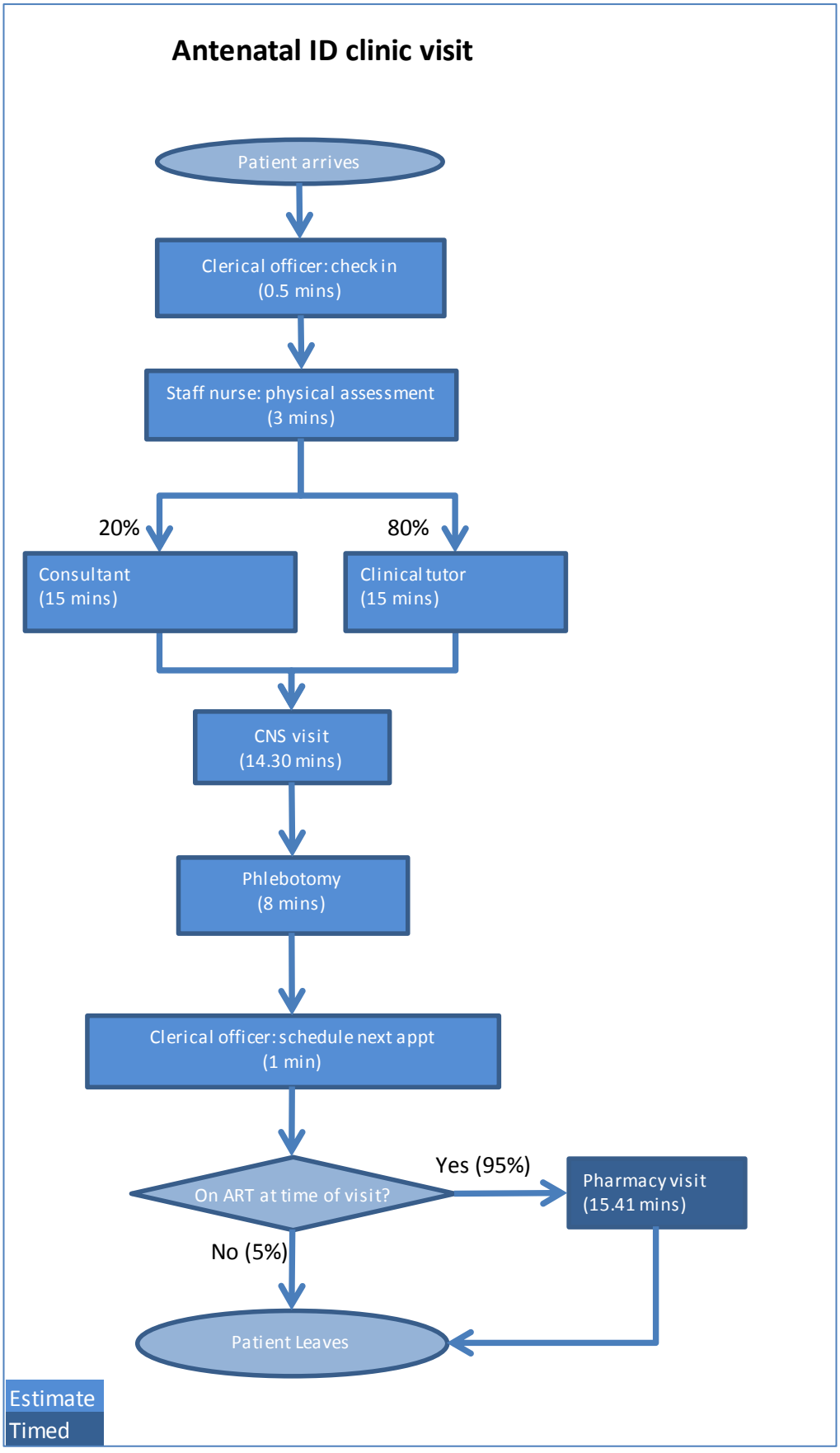
6) Please give details of any important differences, e.g. how services are provided and/or differences in patient populations, between this centre and Cork University Hospital and/or other HIV centres which you think are likely to affect the costs of providing outpatient HIV care in your centre?

7) Any other comments?

Appendix 8. Flow-charts, Cork University Hospital

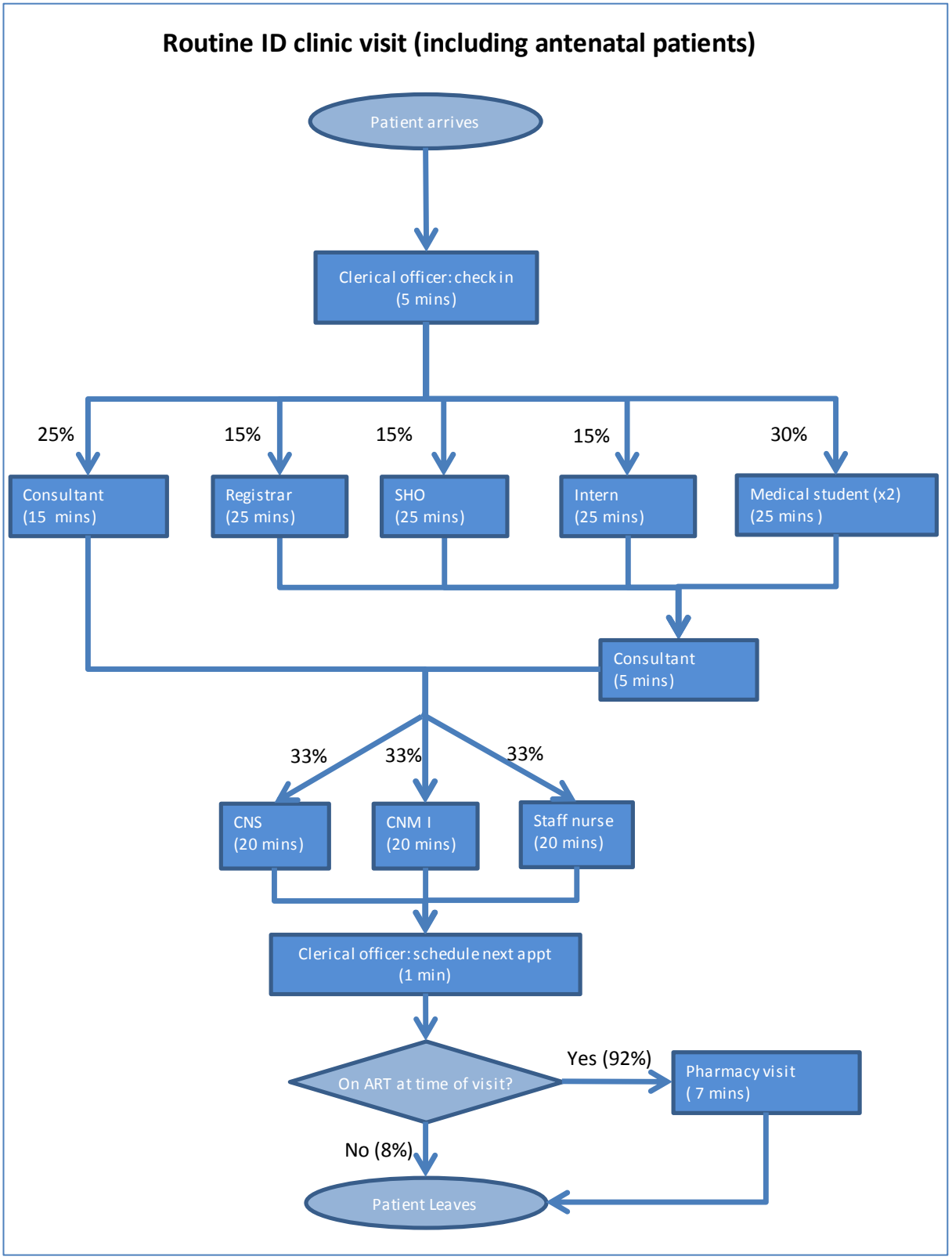


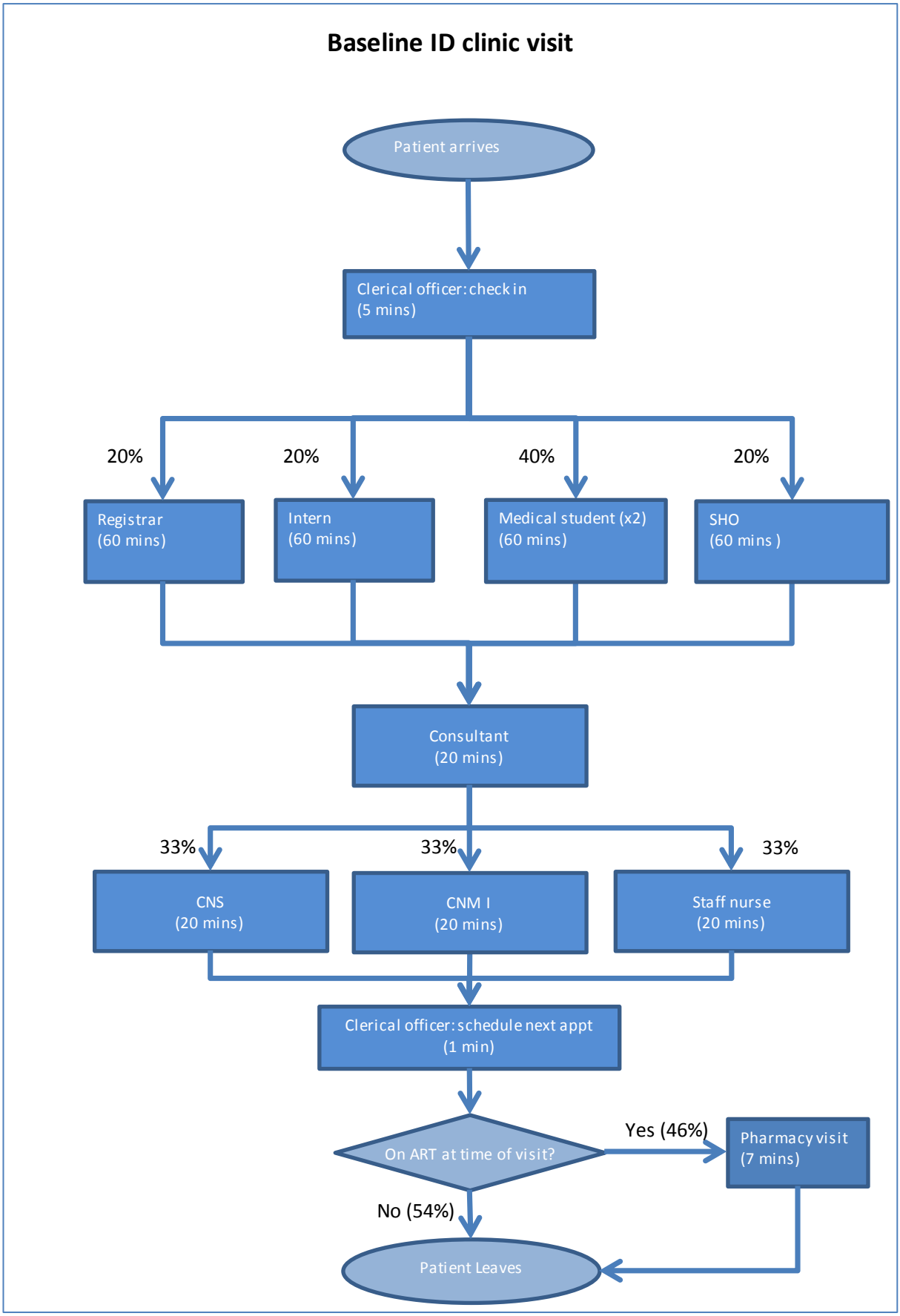

Baseline ID clinic visit
Patient arrives
Clerical officer: check in
(0.5 mins)
Staff nurse: physical
assessment
(3 mins)
45%
45%
10%
Consultant
(25 mins)
Clinical tutor
(25 mins)
Specialist Registrar
(25 mins)
CNS visit
(20 mins)
Phlebotomy
(8 mins)
Clerical officer: schedule next appt
(1 min)
On ART at time of visit?
Yes (46%)
Pharmacy visit
(15.41 mins)
No (54%)
Patient Leaves
Estimate
Timed


Antenatal ID clinic visit
Patient arrives
Clerical officer: check in
(0.5 mins)
Staff nurse: physical assessment
(3 mins)
20%
80%
Consultant
(15 mins)
Clinical tutor
(15 mins)
CNS visit
(14.30 mins)
Phlebotomy
(8 mins)
Clerical officer: schedule next appt
(1 min)
On ART at time of visit?
Yes (95%)
Pharmacy visit
(15.41 mins)
No (5%)
Patient Leaves
Estimate
Timed

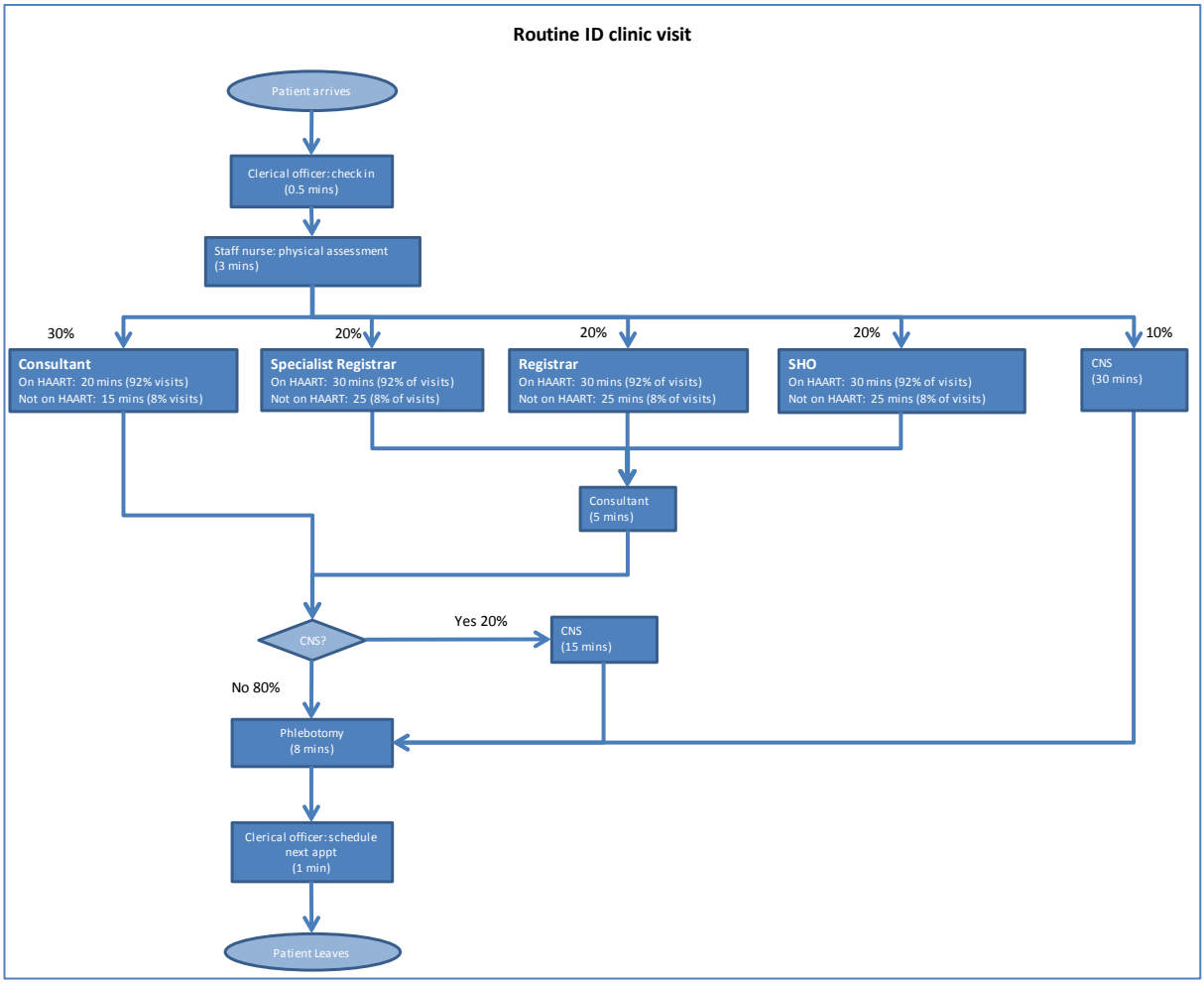
Appendix 9. Visit flow charts by centre

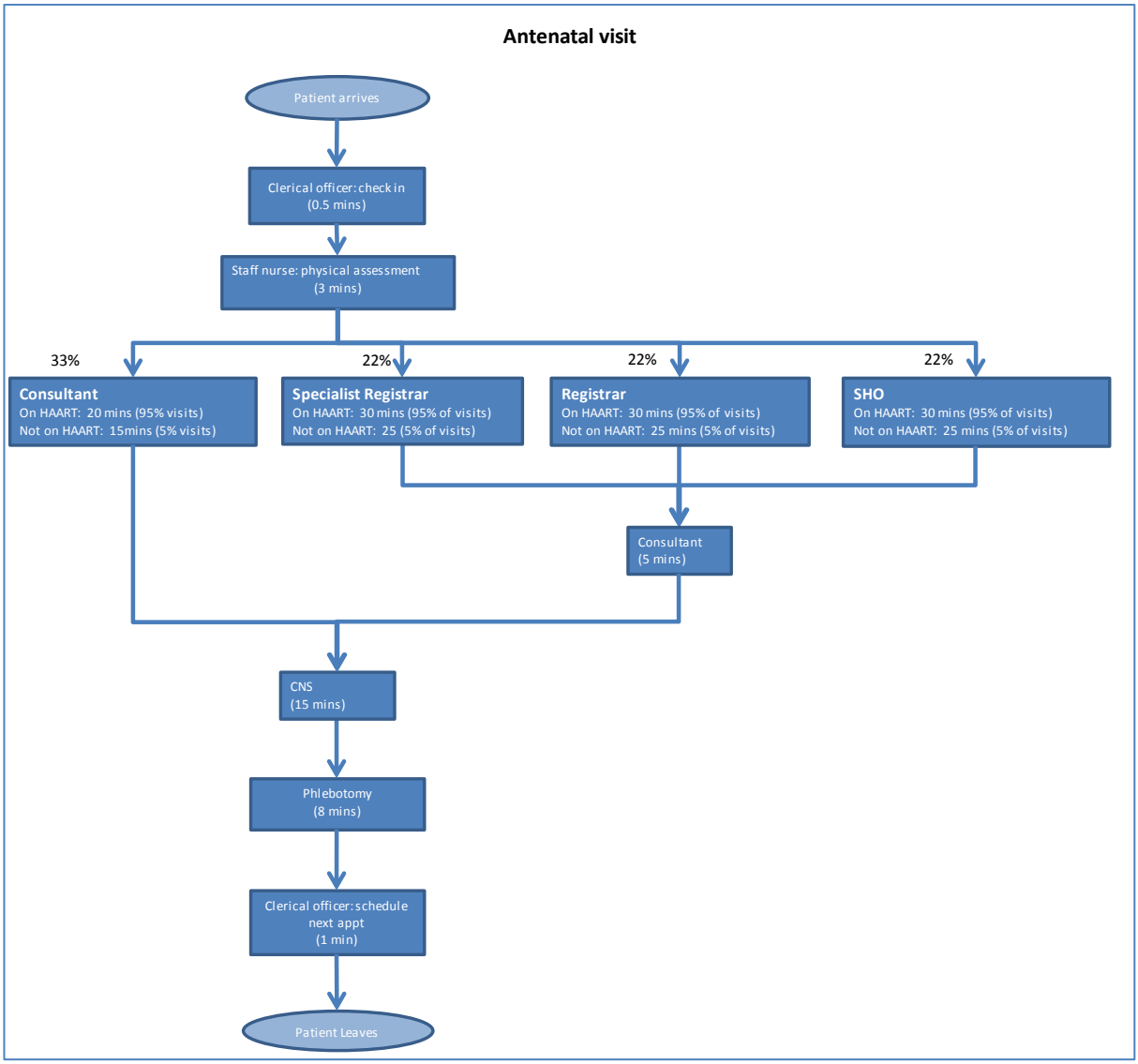
Beaumont Hospital

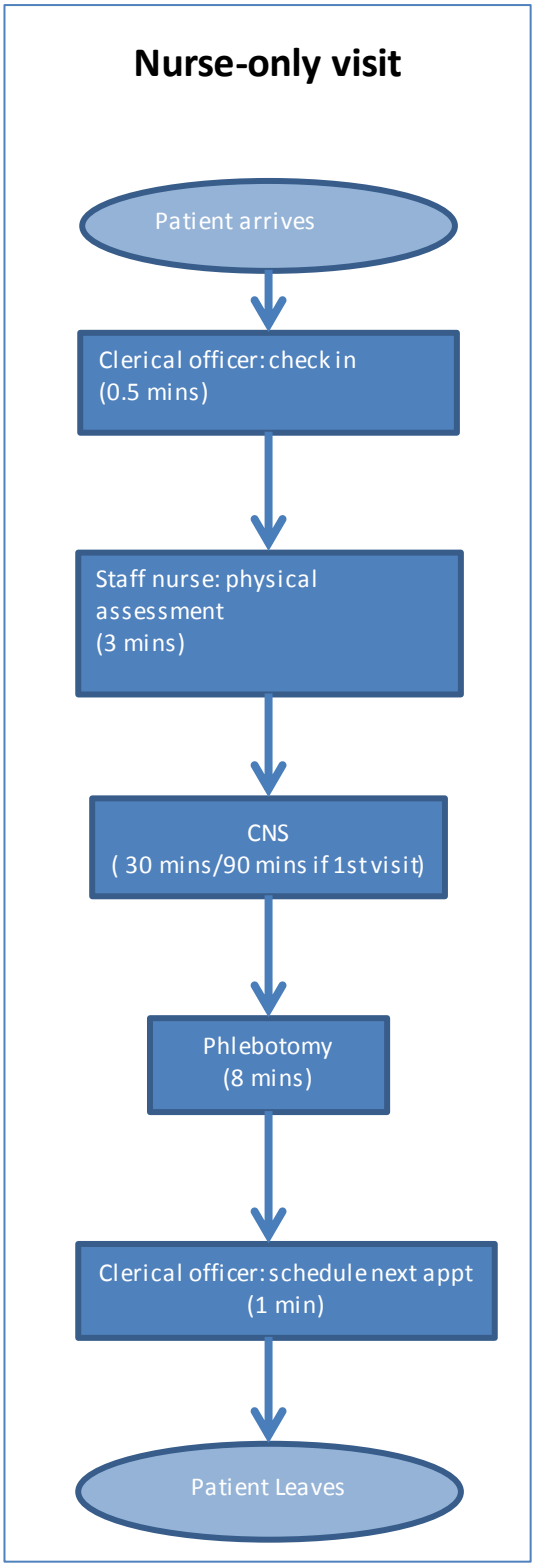


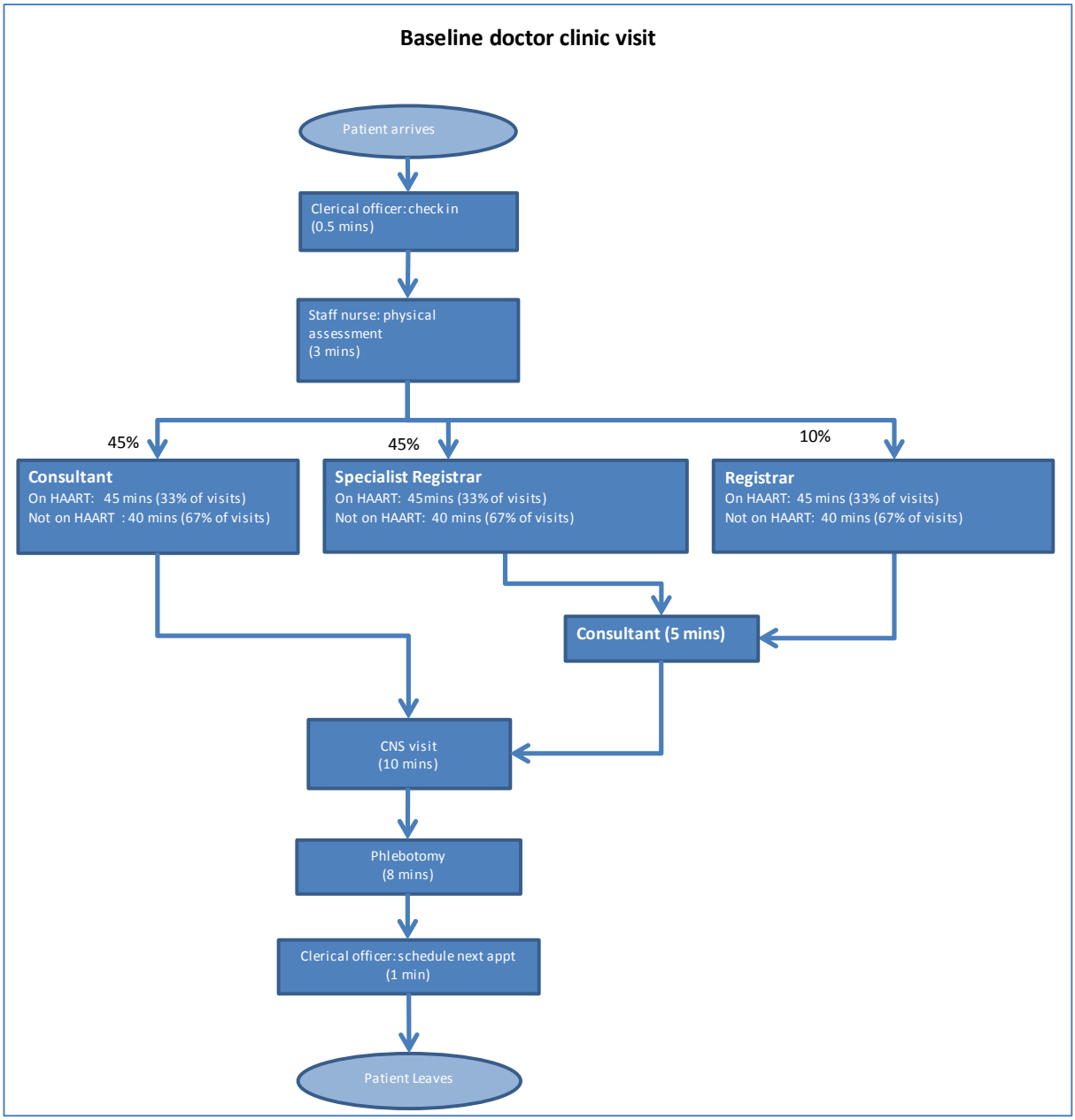

Baseline ID clinic visit
Patient arrives
Clerical officer: check in
(5 mins)
20%
20%
40%
20%
Registrar
(60 mins)
Intern
(60 mins)
Medical student (x2)
(60 mins)
SHO
(60 mins)
Consultant
(20 mins)
33%
33%
33%
CNS
(20 mins)
CNM I
(20 mins)
Staff nurse
(20 mins)
Clerical officer: schedule next appt
(1 min)
On ART at time of visit?
Yes (46%)
Pharmacy visit
(7 mins)
No (54%)
Patient Leaves

University College Hospital Galway

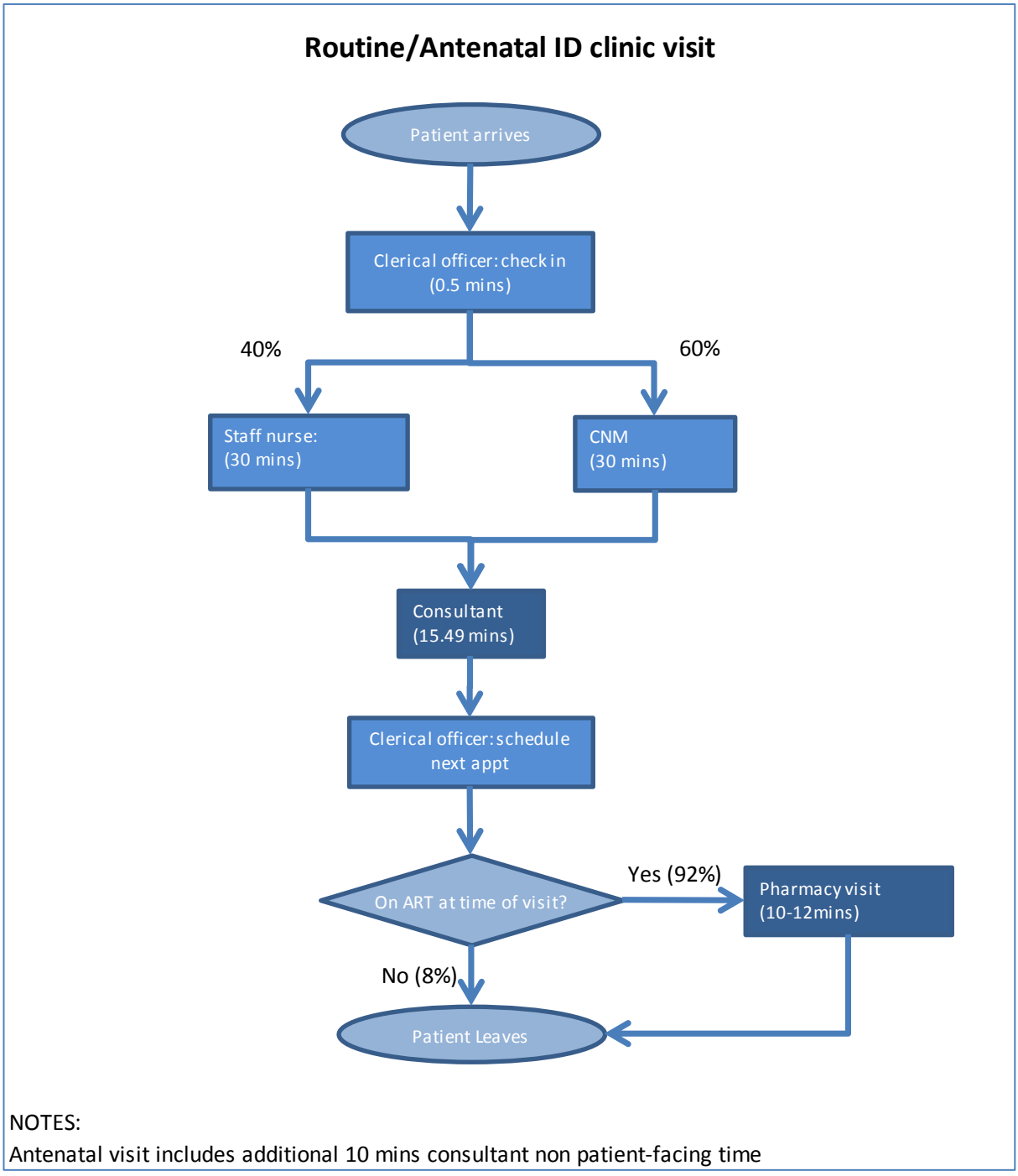



Antenatal visit
Patient arrives
Clerical officer: check in
(0.5 mins)
Staff nurse: physical assessment
(3 mins)
33%
22%
22%
22%
Consultant
On HAART: 20 mins (95% visits)
Not on HAART: 15mins (5% visits)
Specialist Registrar
On HAART: 30 mins (95% of visits)
Not on HAART: 25 (5% of visits)
Registrar
On HAART: 30 mins (95% of visits)
Not on HAART: 25 mins (5% of visits)
SHO
On HAART: 30 mins (95% of visits)
Not on HAART: 25 mins (5% of visits)
Consultant
(5 mins)
CNS
(15 mins)
Phlebotomy
(8 mins)
Clerical officer: schedule
next appt
(1 min)
Patient Leaves


Nurse-only visit
Patient arrives
Clerical officer: check in
(0.5 mins)
Staff nurse: physical
assessment
(3 mins)
CNS
(30 mins/90 mins if 1st visit)
Phlebotomy
(8 mins)
Clerical officer: schedule next appt
(1 min)
Patient Leaves


Baseline doctor clinic visit
Patient arrives
Clerical officer: check in
(0.5 mins)
Staff nurse: physical
assessment
(3 mins)
45%
45%
10%
Consultant
On HAART: 45 mins (33% of visits)
Not on HAART : 40 mins (67% of visits)
Specialist Registrar
On HAART: 45mins (33% of visits)
Not on HAART: 40 mins (67% of visits)
Registrar
On HAART: 45 mins (33% of visits)
Not on HAART: 40 mins (67% of visits)
Consultant (5 mins)
CNS visit
(10 mins)
Phlebotomy
(8 mins)
Clerical officer: schedule next appt
(1 min)
Patient Leaves

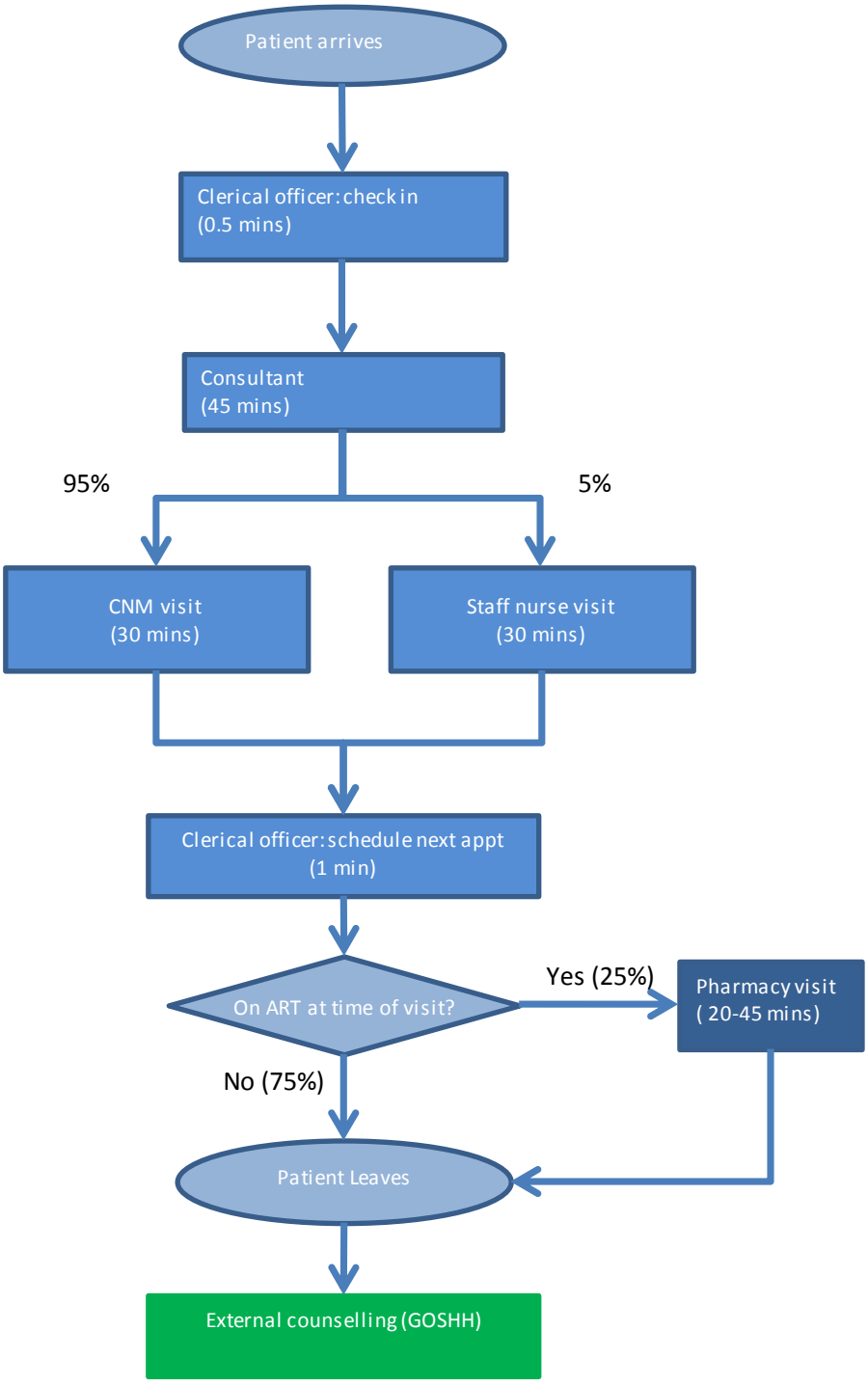
University Hospital Limerick



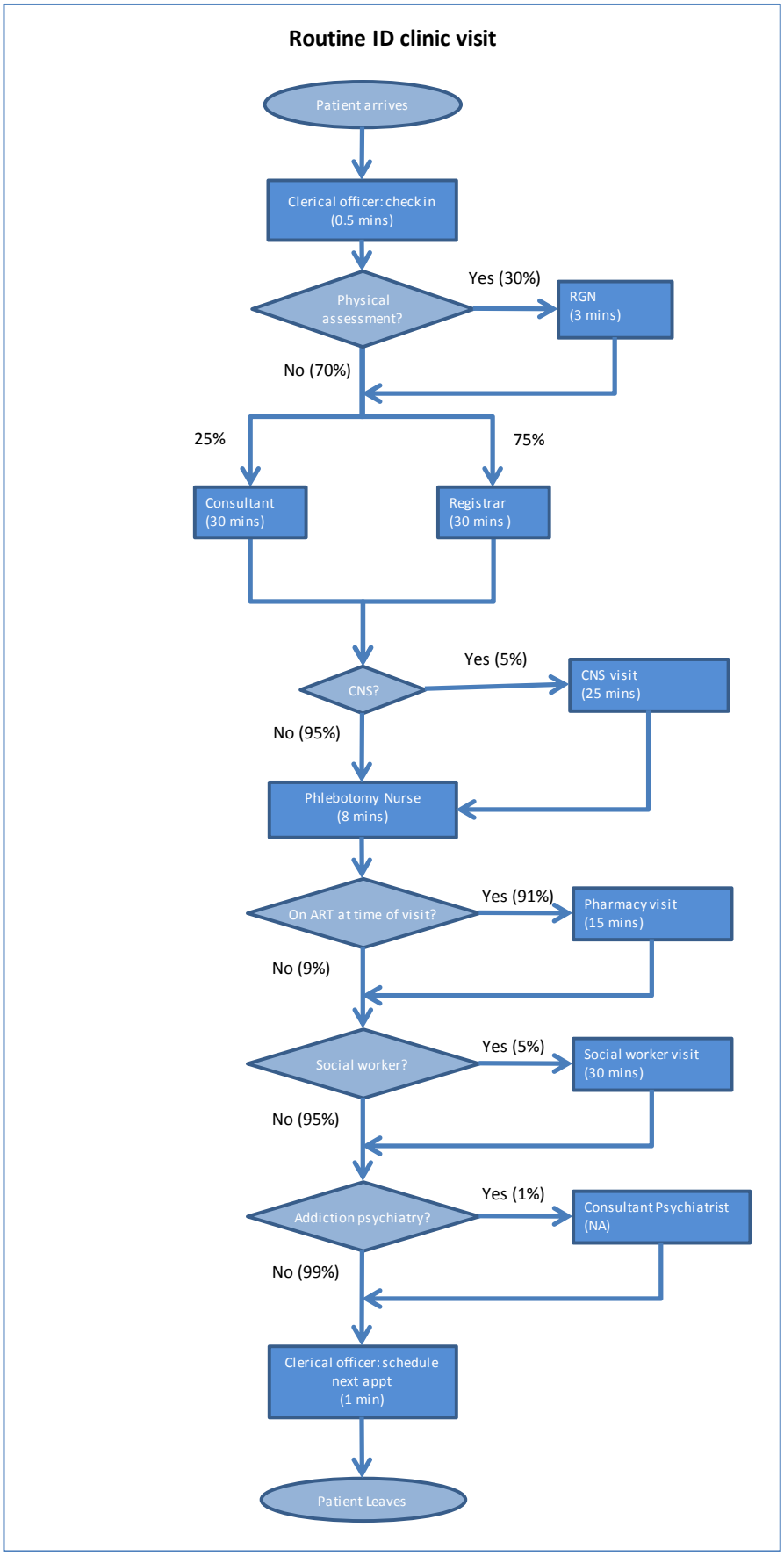
NOTES:
Antenatal visit includes additional 10 mins consultant non patient-facing time

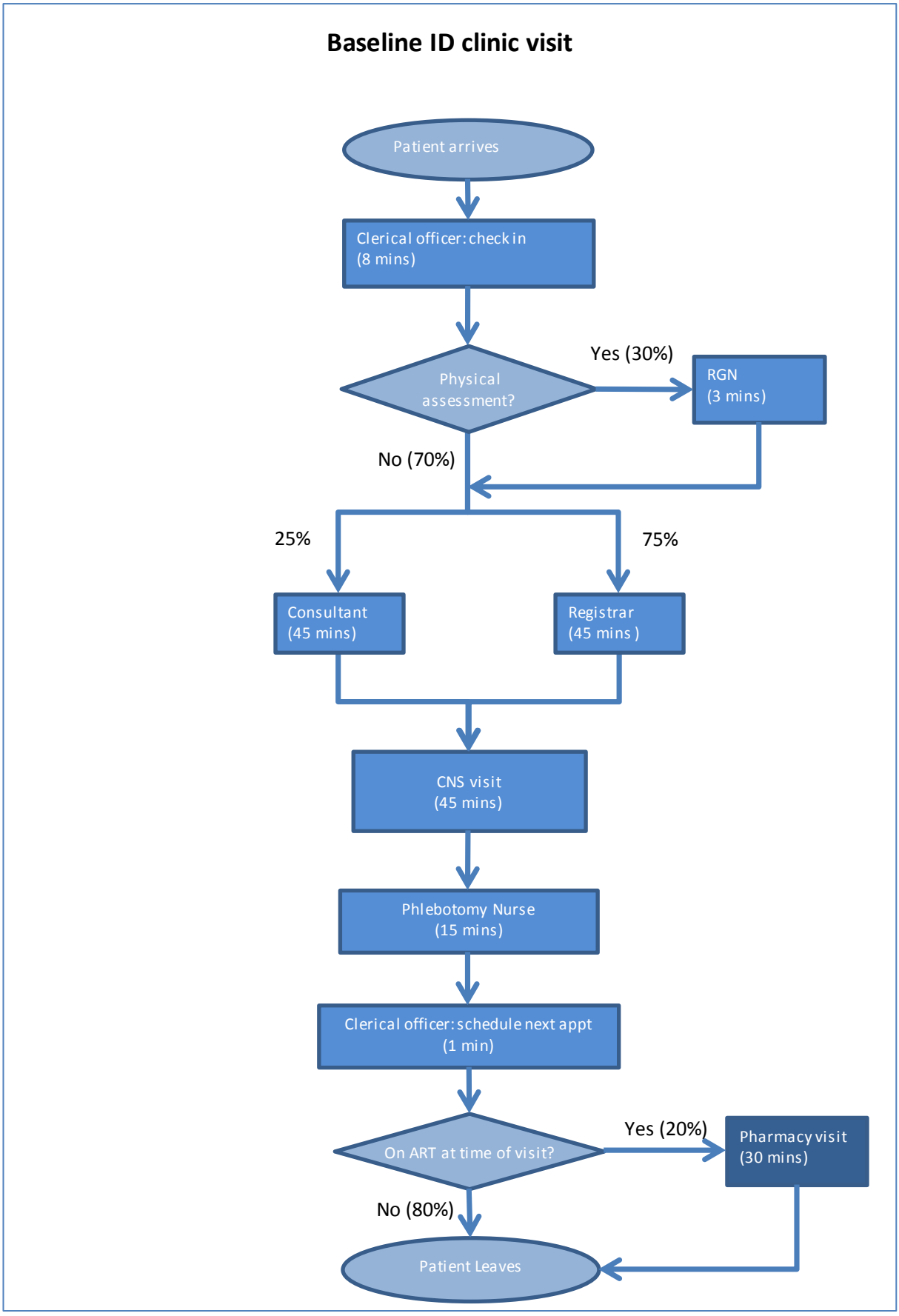
Baseline ID clinic visit

New diagnoses/complex transfers

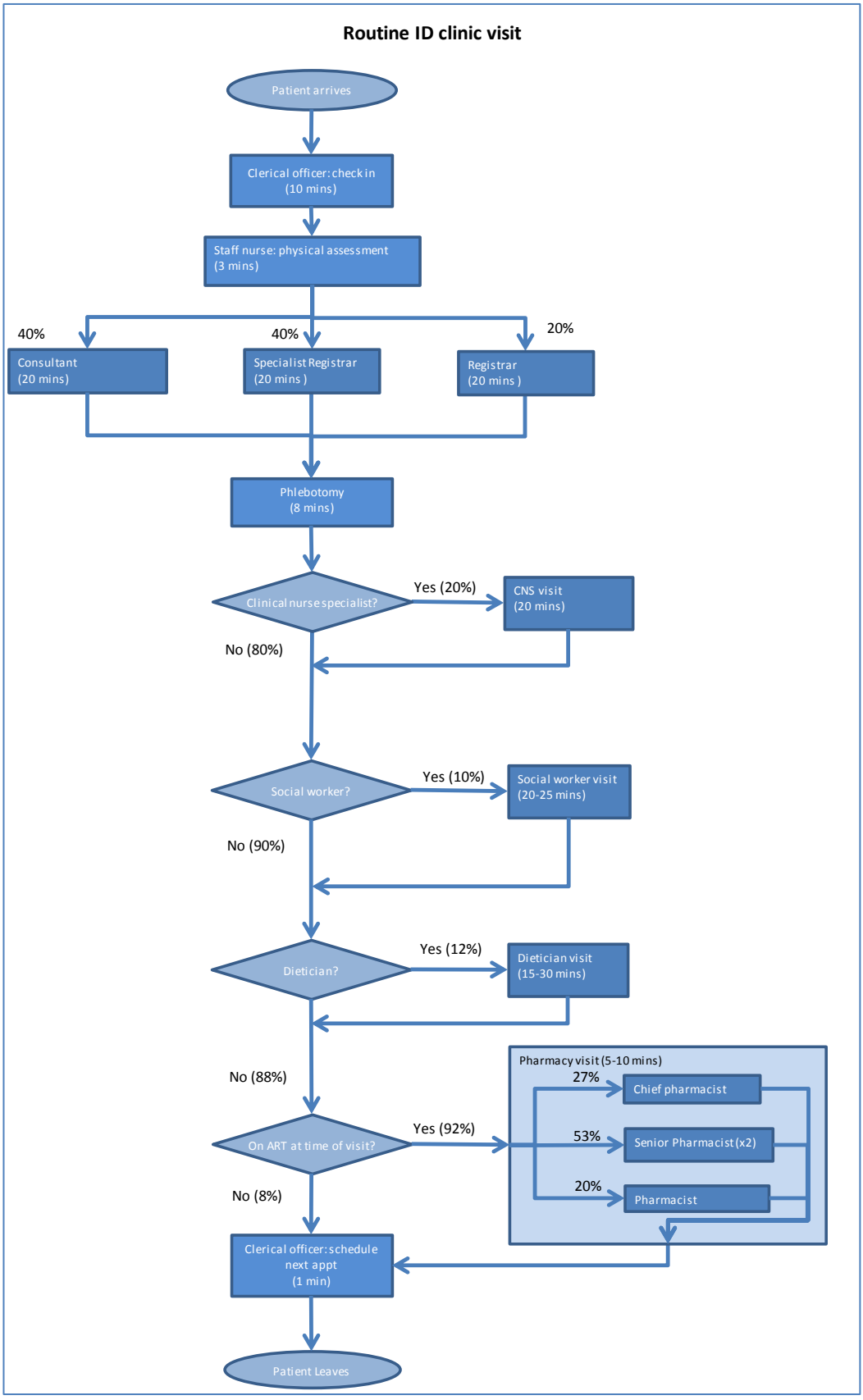


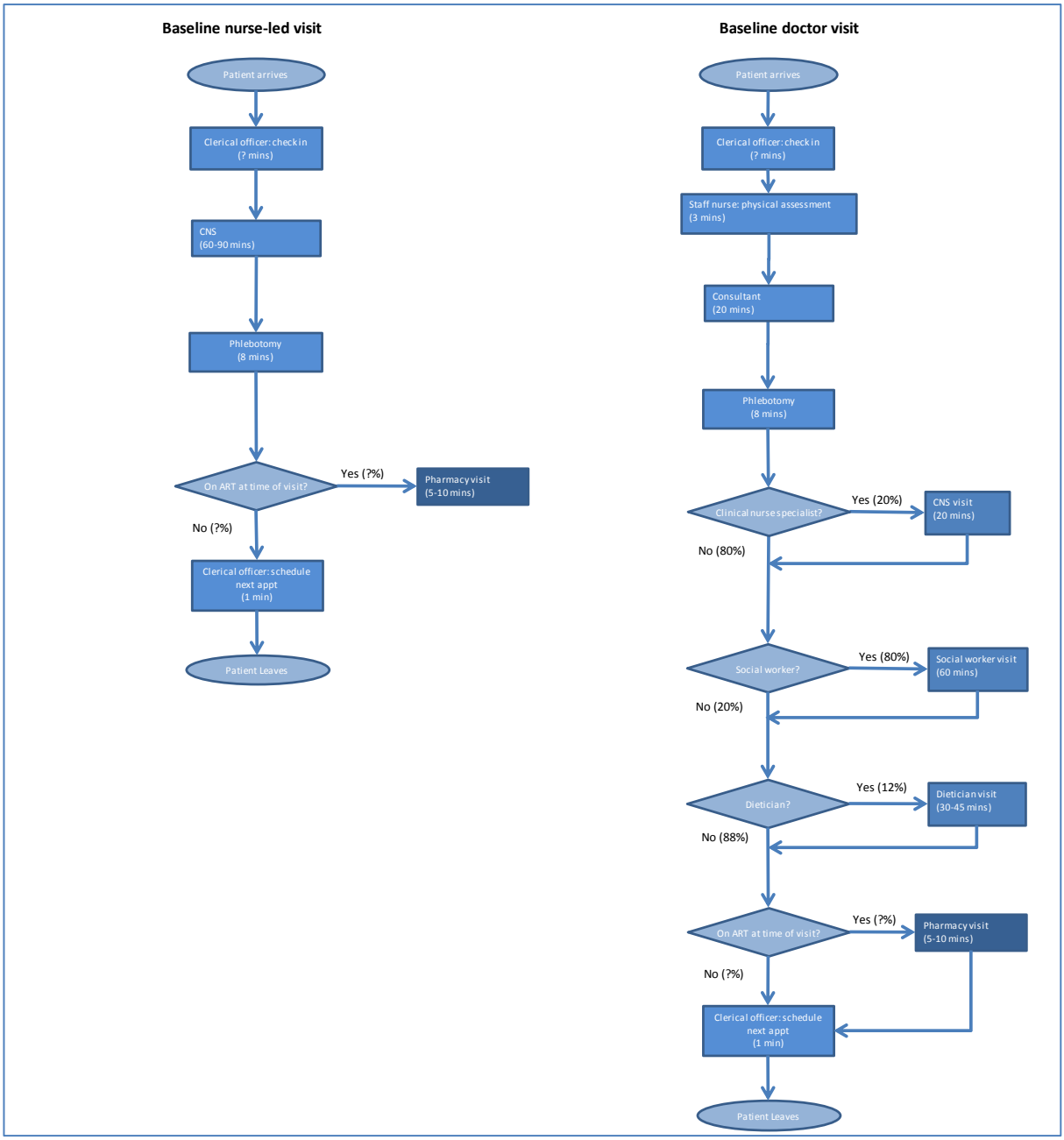
The Mater Misericordiae University Hospital




Baseline ID clinic visit
Patient arrives
Clerical officer: check in
(8 mins)
Physical
assessment?
Yes (30%)
RGN
(3 mins)
No (70%)
25%
75%
Consultant
(45 mins)
Registrar
(45 mins)
CNS visit
(45 mins)
Phlebotomy Nurse
(15 mins)
Clerical officer: schedule next appt
(1 min)
On ART at time of visit?
Yes (20%)
Pharmacy visit
(30 mins)
No (80%)
Patient Leaves

St James's Hospital




Baseline nurse-led visit
Patient arrives
Clerical officer: check in
(? mins)
CNS
(60-90 mins)
Phlebotomy
(8 mins)
On ART at time of visit?
Yes (?%)
Pharmacy visit
(5-10 mins)
No (?%)
Clerical officer: schedule
next appt
(1 min)
Patient Leaves
Baseline doctor visit
Patient arrives
Clerical officer: check in
(? mins)
Staff nurse: physical assessment
(3 mins)
Consultant
(20 mins)
Phlebotomy
(8 mins)
Clinical nurse specialist?
Yes (20%)
CNS visit
(20 mins)
No (80%)
Social worker?
Yes (80%)
Social worker visit
(60 mins)
No (20%)
Dietician?
Yes (12%)
Dietician visit
(30-45 mins)
No (88%)
On ART at time of visit?
Yes (?%)
Pharmacy visit
(5-10 mins)
No (?%)
Clerical officer: schedule
next appt
(1 min)
Patient Leaves