Cause specific mortality, survival and life expectancy in HIV positive people in Scotland

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Drew Millard, Paisley, August 2010.

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Glossary

Term	Meaning
ACP	American College of Physicians
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Therapy
ART-CC	Anti-Retroviral Therapy Collaboration
BASHH	British Association for Sexual Health and HIV
BHIVA	British HIV Association
BTT	Blood/tissue Transfer
CAD	Coronary Artery Disease
cART	combined Anti-Retroviral Therapy
CASCADE	Concerted Action on SeroConversion to AIDS and Death in Europe
CD4	Cluster of Differentiation type 4 T helper cells (Measure: cells per microlitre)
CDC	Centre for Disease Control (in the US)
CI	95% Confidence Interval
CMR	Crude Mortality Rate
CNS	Central Nervous System
COD	Cause of Disease
COHERE	Collaboration of Observational HIV Epidemiological Research Europe
CVD	Cardio-Vascular Disease
D:A:D	The Data Collection on Adverse Events of Anti-HIV Drugs Study
DNA	De-oxyribose Nucleic Acid
DOB	Date of Birth
DOD	Date of Death
EBM	Evidence-Based Medicine
FSRH	Faculty of Sexual and Reproductive Health (Royal College of Obstetricians and Gynaecologists)
GROS	General Registrar Office (Scotland)
HAART	Highly Active Anti-Retroviral Therapy
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immuno-deficiency Virus
HIV+	A person who has been tested for HIV and received a positive result
HL	Hosmer Lemeshow (test of logistic regression model fit)
HMIC	Health Management Information Consortium
HPS	Health Protection Scotland
HPV	Human Papilloma Virus
HRP	High Risk Partner
ICD	International Classification of Diseases
ICD10	International Classification of Diseases tenth revision
ICD9	International Classification of Diseases ninth revision,
ICD9-CM	International Classification of Diseases ninth revision,
IDU	Intravenous Drug User
IHD	Ischemic Heart Disease
KS	Kaposi's Sarcoma

LC	**Lung Cancer**
LCL	**Lower 95% Confidence limit**
LDL	**Low Density Lipoprotein**
LE	**Life Expectancy**
Life expectancy	**'The average number of years an individual of a given age is expected to live if current mortality rates continue to apply. A statistical abstraction based on existing age-specific death rates'[1]**
lipidodystrophy	**Disorder of fat metabolism**
LML	**Log minus Log**
MI	**Myocardial infarction**
Microlitre	**One thousandth of a millilitre, and one millionth of a litre**
Mortality rate	**'An estimate of the portion of a population that dies during a specified period'[1]**
MPH	**Master of Public Health (Postgraduate Degree)**
MSM	**Men who Have Sex with Men**
NHL	**Non-Hodgkin's Lymphoma**
NRTI	**Nucleoside Reverse Transcriptase Inhibitors**
OR	**Odds Ratio**
p	**Probability (statistical significance)**
PCNSL	**Primary Central Nervous system, lymphoma?**
PI	**Protease Inhibitor**
PML	**Primary Multifocal Leucoencephalopathy**
PYLL	**Potential Years of Life Lost**
SC	**Sero-Conversion (to HIV+)**
SD	**Standard Deviation**
SIMD	**Scottish Index of Multiple Deprivation**
SIR	**Standardised Incidence ratio**
SMR	**Standardised Morbidity Ratio**
Soundex code	**A method of coding surnames**
SPSS	**Statistical Package for the Social Sciences**
Survival curve	**'The percentage of the study population still surviving at successive times as long as information is available'[1]**
UCL	**Upper 95% Confidence limit**
UK	**United Kingdom of Great Britain and Northern Ireland**
US	**United States of America**
WHO	**World Health Organisation**

Structured Abstract

Background

There is an increasing population living with an HIV positive diagnosis in Scotland. Mortality has fallen since the introduction of Highly Active Antiretroviral Therapy in 1996.

Aims

To analyse demographic, mortality, survival, life expectancy and cause of death trends over four HAART eras of patient first report from 1981 to 2009, and set their implications in context.

Methods

The Scottish national HIV database was used to explore cause specific mortality, survival and life expectancy.

Results

Most cases were male. Age at first report was early thirties. Mean age at first report increased over time from 29.4 (1989) to 42.1 (2009). Transmission involving infection drug use fell to 5%, sexual transmission rose to 51% for heterosexual and 39% for MSM. Proportions of female, non white, and heterosexual people rose.

Annual Mortality peaked in 1995 at 10%, age standardised mortality reduced, survival time increased, but life expectancy was comparatively low. Adjusted odds of death were statistically significant for era of HAART first report, age, ethnicity, transmission route, and earliest CD4 count. The proportion of deaths with known cause with a primary AIDS-related cause did not fall**.** The proportion with any AIDS condition (mainly AIDS-related infections) rose. AIDS-related survival time decreased.

Conclusions

Survival is increasing. A shift in the health care model is implied by morbidity from non-AIDS illnesses and chronic diseases as the mean age of this growing population rises, but although overall mortality has fallen dramatically the proportion of deaths from AIDS has not fallen post-HAART.

(248 words)

1 Introduction

HIV (Human Immunodeficiency Virus) infection is recognised by the World Health Organisation (WHO) as a pandemic. Worldwide, a total of 33.4 million (31.1–35.8 million) adults and children (0.8% of the world population) were estimated to be living with HIV in 2008.[2] Prevalence was calculated 'using data from sentinel surveillance, surveys and special studies'. Worldwide prevalence has increased by 20% since 2000, but "In 2008, the estimated number of new HIV infections was approximately 30% lower than at the epidemic peak 12 years earlier." Prevalence in Scotland was estimated in 2008 at 0.08% (4,143 cases[3]). Scottish research reports a 'Scottish effect' on wider health involving poor life expectancy and excess mortality by international comparisons.[4-6]

In 2008, one third of HIV positive people were estimated to be unaware of their HIV+ status in Scotland[7] Health Protection Scotland (HPS) estimated a further 2017 people could be infected with HIV in Scotland, making true Scottish prevalence around 0.12%. While this was lower than globally, in Scotland, at 2010, new HIV reports were still increasing[8] and had increased since the 1990's. In combination with decreased mortality from the introduction of HAART in 1996,[9] this added up to a growing population in Scotland who were aging with HIV.

HIV is a retrovirus. Retroviruses use the DNA of host cells they infect to replicate themselves. AIDS (Acquired Immune Deficiency Syndrome) is the late stage of HIV infection, where the immune system is compromised.[10] HIV+ refers to someone who has been tested for the presence of HIV and found to have it. Because change in blood serum is used for the test HIV+ people may also be referred to as people who have undergone Seroconversion (SC) or as 'seroconverters'. AIDS has been defined by the Centre for Disease Control (CDC) in the USA as diagnosis with one or more of a list of conditions known to be strongly associated with HIV infection[11] or a CD4+ (cluster of differentiation 4) cell count of less than 200 CD4+ T-lymphocytes/microlitre. CD4+ cells help other white blood cells fight infection. CD4 cells are gradually destroyed by HIV, reducing in number with time after HIV infection. HAART (Highly Active Antiretroviral Therapy – see below) has a positive effect on CD4 cell count. Sabin (2006) found lower median last CD4 count before death in patients on HAART (68) compared to those not on HAART (167).[12] Those

dying from an HIV-related cause of death had lower CD4 counts than those not. Lower CD4 count before death is a positive outcome in patients with HIV/AIDS.

HAART, where three or more antiretroviral drugs are used in combination, was introduced in the developed world from 1996. HAART has been associated with sharp and continuing reductions in mortality rates in younger age ranges and increases in survival times after a diagnosis with HIV+ infection.[13-15] Much research and clinical attention has added detail to this overall positive picture, but there has been little recent work from Scotland. The detail has covered specific diagnoses[16] and diagnostic groups,[17;18] and whether access to HAART and the effects have been shared between all transmission (or risk) groups and demographic groups.[19]

Three periods of HAART (pre, early and late HAART) informed the data analysis. These periods were based on a US study by Crum (2006).[20] The current study added a fourth 'ultra-active' HAART era to allow inclusion of the period from 2004. The four HAART eras were therefore:

1. Pre HAART : pre-1997,
2. Early HAART: 1997-1999,
3. HAART: 2000-2003 and
4. Ultra active ART: after 2003.

Unless otherwise specified these were HAART eras of first HPS report with HIV.

There were emerging issues around the side effects of HAART and the implications of increased longevity,[21] with evidence being sought on increases in the risk of deaths from non-AIDS causes especially among older HIV+ people.[22-25] For HIV and general health service planning in Scotland, there was a need to know population mortality, survival, and life expectancy trends for people with Acquired Immune Deficiency Syndrome (AIDS)-related conditions and for HIV positive people with non AIDS defining conditions in the context of the Scottish population.

2. Literature Review

2.1 Aims of the literature review

The aims of the literature review were to set the context for analysis of:

- current survival and mortality trends, both overall and for the changing patterns of causes of death, especially from non AIDS defining causes, and

- the relative balance of causes of death, in particular cancer, CVD, trauma and suicide, with reference to the effects of increasing age.

2.2 Search Strategy

Databases searched

- Ovid Medline 1996-2009 (Nov (week 3)
- Ovid Embase 1996-2009 (Nov (week 51)
- All EBM reviews
- HMIC Health Management Information Consortium (November 2009)

Three searches were done, with the expert help of a trained medical librarian at Glasgow University library. The first was a multi-database search of the databases above. Text word title and abstract searches were used. Text words were used in place of keyword searches on advice from the librarian that the former were more focused. The two further searches used the logic from search 1 and Medline and Embase subject headings rather than text words or keywords. They were carried out as single database searches in each of those databases.

Search logic

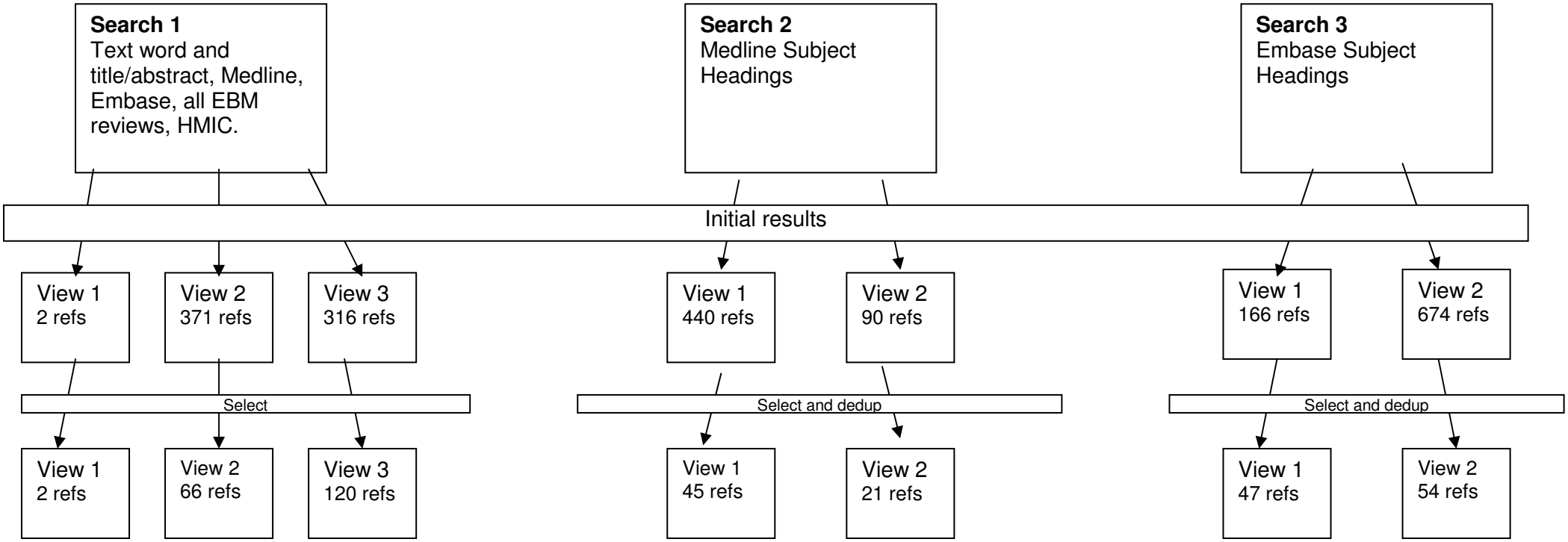
Searches focused on survival/life expectancy and mean age in relation to aging or older HIV or AIDS patients, and cause of death (cancer and CVD) The search strategies are given in full in Appendix 1. The results and abstracts from relevant views were scanned and papers were further selected and downloaded to reference

manager (a bibliographic computer software programme). An informal critical appraisal was made of all papers included in the literature review.

The literature search overview (fig 2.1) below aims to give an impression of the volume of papers and the sifting process. Literature from developing countries, non-English language, rare conditions and about children was excluded. The details of the excluded references were retained as an audit trail.

Reference checks, were made for selected references of interest from the papers found and full papers obtained. There were hand searches of key journals (AIDS), and internet searches of Google and Google Scholar.

Fig 2.1 Literature search strategy overview



Total 355 refs. Selected from 2059 found. Search period 1996-2009 (Dec).
These were the basis of the review, though inclusion of every one of them was not mandatory. For example more recent references were used for points where there were a number of similar references. Review was not limited only to these references. However there were not many additional references as the original search was thorough.

The different views of each search came from selection of results from the strategies when they were applied to titles, abstracts, text words or subject headings depending on the structure of the database used. Each viewpoint is noted in the search strategy in appendix 1.

2.3 Introduction to literature review

Population-based epidemiological studies of survival from a known date of infection were the most appropriate for the aims of the study, but the literature on mortality and survival is heterogeneous: studies may assess survival after different periods of time from diagnosis, which may itself occur at different stages of the disease, and in different contexts.

For even population and disease register based studies, since there is no routine HIV testing on death there is a probability that some die with unknown HIV infection, resulting in selection bias. Treatment based samples and cohort studies (including morbidity) were included where relevant to assessing the general service impact of increasing survival and decreasing mortality as a meaningful and relevant context. Buchacz 2009,[26] for example, saw increasing need for preventive lifestyle changes and screening.

2.4 Overview: Anti-retroviral drugs and increasing survival and decreasing mortality with HIV

A study by Crum (2006) showed total annual death rates peaking in 1995 and a step reduction from 1997.[20] Crum 2006 found increasing mean CD4 counts over eras of HAART.[20]

There is much evidence that survival with HIV increased in most developed countries following the introduction of HAART in 1996.[15;27-30] In Eggers' Swiss cohort,[31] which compared 1988-90, 1991-2, 1993-4 and 1995-6, survival was already increasing before this for CD4 counts below 50 and below 200, although unfortunately a high proportion (25.2%) were lost to follow up. Using direct standardisation instead of Cox proportional hazards models because the proportional hazards assumption did not hold, Lee described the improvement in median survival after AIDS diagnosis from 1984 to 1997.[32] Egger's 2002 study,[33] using the Antiretroviral therapy (ART) collaboration data, retrospectively analysed 13 out of 16 prospective cohorts of over 100 patients with HIV aged 16+ from Europe and North America. Weaknesses of the

study included that the disease may be being diagnosed and treated earlier in the later period, and the development of better treatment for AIDS conditions such as opportunistic infections. Although 3 cohorts were missing a description of the 13 included was given, which helped improve understanding of the level of generalisability.

Dorruci[34] reviewed the effect of treatment on the hazard of death in a cohort of 1535 Italians with a known date of seroconversion (SC) and found when adjusted for year of SC, relative hazard had fallen by nearly 50% in 1997 compared to pre 1991. Seroconversion was defined as a negative HIV test followed by a positive test within two years. This was using a multivariate cox model, Relative Hazard = 0.54; 95% confidence interval, 0.30-0.98. 54% of participants were injecting drug users.

Arnold et al showed in the US, that not all ethnic and other groups have seen the same improvement.[35] Only persons with AIDS diagnosed before 2001 were included to allow two years for mortality outcomes. Possible confounding factors for differences included returning to country of origin when ill especially for the relatively good survival of Latinos - they had 23% lower mortality than whites in 2006. Black people had over twice the mortality rate of whites in 2006. These gaps had increased from 1999.

Sackoff (2006)[36] investigated causes of death in the late (1999-2004) HAART period. Underlying cause was classified into nine major categories, with non HIV related being substance abuse, CVD, cancer, accidents, chronic lower respiratory disease, diabetes mellitus, intentional self harm (suicide) assault (homicide) and nephritis. For 12,715 deaths with known causes of persons with AIDS, c.25% were non HIV-related (therefore not AIDS deaths). Among persons with AIDS the percentage declines from 1999 to 2004 in the rate per 10,000 persons with AIDS were 55% for HIV related (from 458 deaths to 206 deaths) and 34% for non HIV related (from 120 deaths to 79 deaths). The percentage of deaths that were not HIV related rose from 20% to 26%. Mortality was lowest for MSM and highest for IDU. Appropriate statistical tests were used. The strongest clinical predictor of both HIV-related and unrelated death was CD4 count of <50. The count used was the lowest count in the second half of 2004 or within 6 months of death. Advanced age and injection drug use were also important. “Among deaths due to non–HIV-related causes, the 3 leading underlying causes were substance abuse (31.0%), cardiovascular disease (23.8%), and cancer (20.8%), together

accounting for 75.6% of deaths."[37] HIV-related causes were not further broken down into groups.

Deaths were ascertained by regular matching (method not stated) between the HIV reporting system and vital statistics registry. This system was admitted imperfect by the authors as a way to identify cause of death, because based on death certificates, which are subject to recorder error and bias. The New York record linkage system had similarities and differences to the Scottish data system for HIV run by Health Protection Scotland (HPS). The New York HIV/AIDS database is a population based registry containing an estimated 95% of AIDS cases from 1981 and non-AIDS HIV infection from 2000. Scotland covers AIDS and HIV from 1981, but estimates of its population coverage of AIDS cases are not available. While the New York system carries out regular twice yearly linkages between this database and the vital statistics registry for AIDS deaths, in Scotland linkages are carried out ad hoc as needed. The New York system appears to aim to clearly identify the underlying cause of death, while the Scottish linked data contains all causes.

Sackoff's study did not adjust for time since seroconversion (SC) or age at SC, although it gave age standardised mortality. It used lowest CD4 count rather than earliest CD4 count. Earliest CD4 count can be used to adjust to some extent for disease stage, by showing how 'late' was initial presentation.

Sackoff signposts the most important broad groups of non-AIDS and HIV-related deaths but uses only underlying cause of death (though robustly identified) to define AIDS. The CDC definition[11] does not limit itself to underlying cause of death.

Rather than compare time periods, Aracena (2008) et al[38] explicitly compared survival, using Kaplan-Meier methods, from diagnosis, for single, dual and triple therapy (HAART) in Mexico, finding a sevenfold improvement in probability of survival for those on HAART compared to those not. Survival continued to improve with newer forms of HAART.[39] Ewings 2008[40] showed early treatment with HAART improved survival with HIV, hazard ratios for death improved consistently over two year periods from pre 1996 to 2006. The study linked with national mortality data but there is no description of the data linkage method.

The increase in life expectancy in HIV+ people was confirmed in Europe for the period between 1996 and 2005 by the ART collaboration.[41] The study was one of the

largest, including over 40,000 cases in a collaboration of 14 cohorts across Europe and the US. The study observed 2,056 deaths in the study period. The ART collaboration[42] found "The average number of years remaining to be lived at age 20 years was about two-thirds of that in the general population in these countries" There was considerable subgroup variation. The study had many strengths, including following up patients whether or not they stayed on ART, so including the tolerability of ART in the overall measure of effectiveness. This study also measured changes in mortality rates: "crude mortality rates decreased from 16.3 deaths per 1000 person-years in 1996-99 to 10.0 deaths per 1000 person-years in 2003-05. Potential years of life lost per 1000 person-years also decreased over the same time, from 366 to 189 years." This suggested increasing survival time, which could have been associated with refinements to HAART.

Weber[43] found liver related deaths were the most frequent non-AIDS related cause, (14.5% of deaths in HIV+ people). They largely resulted from Hepatitis B or C infection associated with injecting drug use. A potential confounder, alcohol intake, was not measured. These deaths were also associated with increased age. Battegay in a 2009 review[44] (giving no search or quality criteria) suggests co-morbidities like hepatitis and cancers are increasingly important in the aging population with HIV.

To summarise, overall mortality had decreased and survival had increased in HIV positive people in the post HAART compared to the pre-HAART period, but there were suggestions of increasing importance of non-AIDS conditions.

2.5 Changes in mortality and survival for AIDS defining causes of death

The well designed US study by Crum (2006) found 80% of 1,224 deaths occurring in a cohort of 4,241 participants from 1990 to 2003 were attributable to AIDS pre-HAART (1990-96), 65% early HAART (1997-1999) and 56% in late HAART (2000-2003). In an earlier study from Bordeaux, France, which used a regional hospital based information system with annual searches for patients lost to follow up, (helping to avoid selection bias). AIDS related events were no longer the major causes of death for HIV+ patients dying between 1998-99 (Bonnet 2002).[17] A 2006 study by Weber[43] (using person years) showed deaths with AIDS-defining causes among

HIV+ people Dec. 1999 - Feb. 2004 were down to one third of the total. Battegay[45] reported that this better survival was related to initiation of HAART at higher CD4 counts (350 or less), with other studies suggesting a CD4 of <350 as a threshold giving further reductions in mortality.

Some cancers were classified as AIDS–defining. These were Kaposi's Sarcoma (KS) and Non Hodgkin's Lymphoma (NHL), invasive cervical, and Burkitt's lymphoma.[11] Bower in a 2006 review[18] found that the incidence of AIDS defining cancers had reduced and survival increased post-HAART (as did Gingues[46] for KS and NHL in a cross sectional comparison study). Yet the prognosis for the HPV associated cancers (cervical and anal) and other non-AIDS defining cancers had not improved as much. Bower (2005)[47] in a small prospective disease cohort study of 215 patients (from the Chelsea and Westminster cohort) with AIDS related NHL, tested the validity of the International Prognostic index for lymphomas, finding risk groups and CD4+ count provided further independent prognostic information for NHL. However, different HAART regimes were potential confounders.

In conclusion to this section, deaths from AIDS-defining conditions have reduced since the introduction of HAART.

2.6 Non AIDS Cancer

A lower CD4 count is increasingly recognised as associated with risk for non-AIDS defining cancers (Clifford 2009).[48] Anal cancer is increased around 30-fold in men with HIV infection in comparison to those without HIV[49] (cervical cancer is increased about six fold), Hodgkin's lymphoma is increased about ten fold.[50;51] Anal cancer incidence has also increased post HAART.[52] D'Souza (2008) using a nested case control study (appropriate for such a rare outcome) compared incidence of anal cancer for HIV positive and negative men by comparing 22 cases of anal cancer among HIV+ MSM with controls of 6 cases of anal cancer among HIV negative MSM. The denominators (total for HIV+ men and total for HIV- men) were not given. There was higher incidence within the cohort per 100,000 person years in HIV+ compared to HIV negative MSM. The long follow up meant the reasons for censoring varied between those recruited earlier and those recruited later into the study, which may have introduced a form of historical bias. D'Souza speculated that the increase found in HIV+ men's incidence of anal cancer is caused by increased survival with HAART

which “may allow for sufficient time for human papilloma virus associated anal dysplasias to develop into malignancies.”[53]

In an HIV+ prospective French cohort enrolled in 1997-1999 who were naive to Protease inhibitors (PIs), Ferry et al 2009[54] found that over a follow up period of more than seven years, non-AIDS events were more frequent than both AIDS defining and combined ART (cART) related events. Events cART related included adverse reactions but the unquantified possibility of cART related non-AIDS events could constitute an information bias. Since interrupted cART led to greater likelihood of severe events, Ferry et al concluded continuous cART protected against morbidity from non-AIDS events generally, including cancer. That may not be justified as there could be unknown confounders such as non adherence to therapy, related to both interruption of cART and severe events. The events, mainly bacterial infections, were not rated for severity, and there was no control group to allow comparison with the non HIV+ population, or with the general population.

HIV infection may make cigarette smokers more prone to aerodigestive cancers, but causes were not clear (Haigentz 2005).[55] Other studies suggested HPV infection, though very common, was reactivated at low CD4 count,[56] and played a role for example in cervical cancer in HIV.[57] In the UK, annual cervical screening is recommended by the joint British Association for Sexual Health and HIV (BASHH), British HIV Association (BHIVA) and Faculty of Sexual and Reproductive Health of the Royal College of Obstetricians and Gynaecologists (FSRH) guidelines for HIV+ women.[58;59] Burkitt’s lymphoma is an AIDS-defining illness in HIV+ people, but is related to a form of herpes called the Epstein-Barr virus.

Lung cancer (LC) incidence was higher in HIV+ people.[60] Respiratory cancer survival time improved in the HAART era.[61] In a review (no strategy given) by Bazoes (2008)[62] increased LC in HIV+ people was found not just related to smoking. Bazoes concluded HAART may have improved the outcomes in lung cancer in HIV+ people. A study in South east England[63] found an eight fold increase in the incidence of LC between the periods 1986-1995 and 1996-2001. Lavole (2006)[64] reviewing this literature noted the incidence of LC in HIV+ people was higher than in the general population, and higher smoking levels did not fully explain that. Standardised incidence rates (SIRs) were used to increase validity of comparison, and studies’ estimates of risk were critiqued, but there is no indication of study selection methods. Age at diagnosis was about 45 years and prognosis was poorer than in the general

population. Some evidence has suggested Hepatitis is connected to cancers in HIV.[65] Bonnet (2008), reviewing the same issue (no strategy given) mentioned a need for viral co-infection management, e.g. hepatitis.[66]

Crum (2006)[20] did not distinguish AIDS and non AIDS cancer, but found the proportion of deaths attributable to cancer peaked in 1996.

In brief, non AIDS defining cancer incidence and mortality have improved less since HAART introduction than AIDS defining cancers, and now make up a larger proportion of the smaller number of total deaths.

2.7 Co-morbidity

Comorbidities in the patients may be related to transmission routes and lifestyle, and like them be systematically different between the pre and post HAART periods. For example Hepatitis (can be related to drug injecting)[67] anal cancer (can be HPV-related),[18;53;68] lung cancer (can be smoking related)[62;64;69] and liver disease (can be alcohol and hepatitis related)[70;71] Although Egger (2002) states the proportion of injecting drug users (19%) in the ART cohort, it and other comorbidities are not stated for the comparison with a pre-HAART cohort from the Multicenter AIDS Cohort Study (MACS) in the US,[72] but the cohort was all MSM, so different from Egger's study. The relatively short follow up period for Egger (3 years from starting HAART) was an unavoidable weakness of the study, but the study was large, with 24,310 person years of follow up of 12,574 patients, and used standardised methods of data collection. A 2005 study[73] found diabetes was increased fourfold in men with HIV on HAART compared to HIV negative men.

Aging haemophilia patients were confirmed more likely than younger ones to be co-infected with HIV and or Hepatitis C in a review by Mauser-Bunschoten (2009).[74] This was primarily owing to transfusion using infected blood between 1978 and 1986.

In summary, as well as more non-AIDS conditions, increasing comorbidities are reportedly more likely with increasing survival.

2.8 HAART, Lipid disorder and Non-AIDS CVD

Acute MI and IHD rates have been shown to be between 75% higher and twice as high in HIV positive people than in the general population.[75;76] A review by Martinez 2009[77] which categorised papers at three levels of interest, suggested CVD incidence in HAART patients was low, but higher than in the general population. The main element of the increased CVD risk in HIV+ patients was owing to traditional CVD risk factors being more prevalent in this group, followed in importance by HIV, then the type of ART.

Khunnawat 2008[78] found coronary artery disease, (CAD), had been increasingly reported as linked to Protease Inhibitors (PIs), an element of some HAART regimens, although Bozzette (2003)[79] concluded that an increase in CVD events did not affect overall mortality in these patients. However this was a sample of veterans from the armed forces, which may not be fully representative of the US population. Farrugia 2009[80] in a review with no search strategy given, found increased prevalence of atherosclerosis in HIV patients. The authors suggested that:

1. HIV was an independent risk factor,
2. HAART affected traditional risk factors or was a risk in its own right, or
3. the HIV label identified a population subgroup with higher prevalence of traditional CVD risk factors.

Farrugia concluded all these played a part in the increased prevalence. Without demonstrating a causal link, Grunfeld et al had shown in 1991 that HIV was associated with an adverse lipid profile, specifically hypertriglyceridemia found in AIDS.

Atherosclerosis

There is evidence of twofold effects of HAART on atherosclerosis, both increasing (by elevating LDL cholesterol) and reducing risk (by impairing HIV replication).[81-84] Battegay et al 2009,[85] reviewing lipid disorders and CVD in HAART patients found it difficult to assess the net effect of HAART on CVD risk for HIV+ people, but mentioned that abacivir (an NRTI) was associated with increased risk of MI. Recent BHIVA guidelines urge caution in prescribing abacivir in patients with high CV risk.[86] Although low CD4 count was the biggest risk factor for sub-clinical carotid

atherosclerosis in these patients, “the prevalence of coronary artery calcification was marginally increased only among long-term [HAART] users.”[86]

Calza 2009[87] in a small cross sectional study found raised incidence of atherosclerotic plaques in patients on HAART for 3 years plus, compared to HAART-naïve patients. Kaplan et al (2008)[88] found low CD4 count was the most robust predictor of carotid atherosclerosis beyond traditional risk factors in HIV+ men and women. They found only a borderline association between PI therapy and carotid atherosclerosis, but the study had relatively small numbers in comparison with other population-based studies in this area. Cotter 2003,[89] reviewed rising concerns about increased CVD in HIV+ people on HAART, and speculated that less CVD toxic HAART regimes would be needed in future, and reported use of anabolic steroids and cocaine as CVD risks in the HIV+ population. Mooser[90] in a discussion paper reporting the position in 2003 cites age as the most important risk factor for CVD, and says the atherosclerosis risk is higher for HIV+ than for HIV- people but that from logistic regression analysis reported elsewhere this was not attributable to HAART per se.

Calza (2008),[91] reviewed risk mechanisms and management for atherosclerosis and heart disease, and suggested CVD risk will need to be annually assessed in HIV+ patients on HAART. Guidelines from New York State Department of Health AIDS Institute recommended this in 2007,[92] and it is a matter under debate at BHIVA.[93]

Khunnawat[78] suggested atherosclerosis and lipodystrophy were potential mechanisms for increased CV risk. Khunnawat reported hypertension was associated with HAART related metabolic syndrome. Unfortunately Khunnawat’s review gives no indication of methods used for the selection or appraisal of papers. A review by Barbaro (2006) found lipid disorder was related to HAART, but there was no consistent association with CV risk.[94] Barbaro’s review gave no search criteria and used no formal meta-analysis. Three quarters of those with lipidodystrophy had raised blood pressure, in comparison to a quarter before HAART according to Sattler (2001)[95] who controlled for family history of hypertension (using logistic regression), but was hampered by the lack of an agreed case definition for lipidodystrophy.

A recent review (no strategy, but tabulated findings from eight HAART trials with CV disease endpoints) suggested the HIV virus itself may cause atherosclerosis through inflammatory effects, which become evident with increased survival resulting from

HAART, but acknowledged that many factors are at work and that some ART may be intrinsically proatherosclerotic.[80]

CVD events

Bozzette[96] found no significant difference in hazard ratio of a cardiovascular event between patients on HAART and those on no therapy after up to 72 months of exposure. This was in 41,213 HIV+ male US veterans from 1993 to 2003. Bozzette argued (surprisingly) that while it needs to be taken into account in individual case management, a CVD event is not a public health risk. CVD event risk increased with age. Bozzette did not compare CVD events risk in patients with HIV with the general population, which would have given a better indication of the public health implications of the increased longevity resulting from HAART. The US veterans may have been less or more prone to CVD risk than other HIV+ people.

The D:A:D study[97;98] aimed to "assess the incidence of myocardial infarction among HIV/AIDS patients who are receiving anti-retroviral therapy." It had more than 35,000 participants and was a large multinational study of 11 cohorts with a power calculation designed to detect a two fold increase in risk of MI between two equal groups. It has resulted in a number of publications. Calza 2009 et al[99] discussed recent findings from the D:A:D study of increased risk of MI in patients treated with two specific HAART NRTI drugs (abacivir and didanosine), not present 6 months after cessation of therapy.(D:A:D Study group 2008).[100] Their results have been described as highly controversial[101] The D:A:D study is funded from diverse sources including commercial (drug companies) and non-commercial,[102] which suggests vested interests may be involved in challenging the increased MI risk.

Bozette 2003[79] suggested higher median age was a reason for increased cerebro-vascular complications, a review by Monforte,[103] added HAART to this, but Calza's more recent evidence strengthened the view that age was not the only factor affecting cardiovascular disease in general in HIV+ patients on HAART. Mary-Krause (2003)[104] found a duration related association between MI and protease treatment. Risk increased by 42% per 10 years of age. There was a suggestion (needing further follow up to confirm) of dose response relationship between person years spent on HAART and MI risk. This study used a cohort of 73,336 French patients registered up to the end of 1999, followed up for a median 32 months, and verified 66 MI deaths reported using hospital questionnaires.

A review by Lo 2008[105] suggested that although more research is required, HIV and related inflammatory responses of themselves increase risk of CVD. This study critiqued the methodology of the studies reviewed as appropriate, for example whether studies included smoking data, and controlled for confounding factors such as HIV+ patients being more likely to be on lipid lowering therapy than control groups.

Screening

Lipschultz (2003)[106] in a review of monitoring and therapy for CV risk factors in HIV+ patients recommended "routine echocardiography for HIV-infected patients". The review made no mention of study selection criteria, search strategies or standardisation of measures. Such screening would have significant cost implications, which were not addressed, and there was no assessment of the likely screening sensitivity (ability to detect true positives as a percent of all positives screened).

To summarise, the issues here were whether comorbidity and mortality from non-AIDS conditions was really increasing or whether this was only apparent because they made up a larger proportion of an overall smaller number of deaths, and if so whether this was related to longer survival, giving the condition longer to appear. Further issues included whether these conditions were relatively more frequent in HIV+ than in HIV negative people, whether they were related to HAART therapy, and whether they increased in incidence with older age to a greater degree than in the general population. Service implications included suggestions for regular screening of HIV+ people for various non-AIDS conditions.

2.9 Aging with HIV – Morbidity, health improvement, co-morbidity, prevention issues, and adherence

The US hospitalisation rates for over 50s with HIV increased between 1996 and 2000, while decreasing for 18-30 year olds (Gebo 2005).[107] There were increased toxic effects from HAART and reduced immunologic benefit, greater comorbidity and higher mortality in older people. Gebo's study was a series of three cross sectional

analyses. Cross sectional studies do not follow up individual cases so cannot assess survival. Aging with HIV may already be with us to a greater extent than reflected in HIV databases. Nguyen reported a 1995 US study that found 6.2% of men and 8.9% of women over 60 who were hospitalised were HIV positive.[108]

The Health Protection Agency (HPA) for England Wales and Northern Ireland recently reported that the over 50's HIV infection rate had more than doubled from 2000 to 2007, 48% were late presenters compared to 33% of younger adults.[109] HIV Scotland estimated for 2008[110] that assuming one third of those infected with HIV were unaware of their status, 2017 people in Scotland could be infected with HIV without knowing it.

A small US study by Greenbaum 2008[111] confirmed much of this, but found reduced infections in older people. The Greenbaum study carried out a sensitivity analysis using an intention to treat analysis for each endpoint. The COHERE group[112] (a collaboration of 33 European cohorts including nearly 50,000 HIV+ patients starting HAART from 1998-2006) supported Greenbaum et al's findings. Results could not be adjusted for hepatitis and there was some collinearity (interaction) between risk group and age, which was not adjusted for.

A reanalysis of data on 13 030 HIV+ individuals from 38 studies in 15 countries by Babiker (2000)[113] found 'Mortality and AIDS incidence increased strongly with time since SC and age at SC.' A strength was use in mortality calculations of person years at risk from entering the study rather than from seroconversion only. Those older at diagnosis perhaps waited longer to get treatment, or as Chiao (1999)[114] suggested, were more likely to be initially misdiagnosed. Manfredi (2002)[23] confirmed the elderly living with HIV were diagnosed late or not at all, and there were worse outcomes for elderly women and minority groups. Manfredi (2004)[25] reported mean age was progressively rising and life expectancy for HIV+ people was close to the general population, but HAART effects were blunted for immunological recovery for older compared to younger people. Earlier initiation of HAART was related to earlier diagnosis and associated with lower risk of death according to a study of patients receiving it at higher CD4+ thresholds.[115] There was no assessment of the effect on quality adjusted life years, which would have been relevant as HAART had significant side effects.

Late diagnosis was raised by Lucas[116] in 2008 as potentially the largest remediable factor for HIV related death in a review of 387 deaths of adults with HIV reported by 133 UK clinical centres between 1 October 2004 and 30 Sept 2005. Late diagnosis accounted for 24% of deaths. However, data were based on subjective clinician reports. Neaton (2008)[117] found CD4 count <250 was best used as a guide, but once started, continuous HAART therapy was better (had lower all-cause mortality) than CD4 count dependent episodic HAART use.[117] The study was not a meta-analysis, but did critically appraise the papers, giving greater credence to larger studies (SMART[118] in particular). In 2004, Dougan,[119] reviewing data from three HIV surveillance systems from 1997-2001 in England Wales and Northern Ireland suggested that age seemed related to late diagnosis especially in heterosexual women.

A review by Nguyen 2008 (no strategy given) pointed up that while "some studies suggest that medication adherence may be improved in the older HIV-infected patient, substance abuse and cognitive dysfunction may contribute to poor adherence." Polypharmacy was an issue for older people, and Nguyen found it contributed to poor adherence.[120]

In summary, issues in relation to aging were weaker response to HAART in terms of immunological benefit, greater susceptibility to side effects of HAART, possible increases in neurocognitive conditions, other clinical events, faster progression to AIDS. Particularly urgently, there was a possible need for earlier diagnosis, since greater age at SC was related to poorer prognosis. There were perhaps particular issues for older women with HIV.

2.10 Mortality with HIV in Scotland

New AIDS cases and deaths fell in Scotland with the introduction of HAART in1996, with 75 deaths in 1995 reducing to 24 in 1997.(Allardice 1998)[9] In the same study, a separate longitudinal analysis increased causal evidence as it showed a highly significant effect of ART on increasing CD4 count (dose response relationship), especially for triple and quadruple therapy. AIDS related dementia was suggested to be more severe (significant in mortality risk) than previously thought, in Scottish research by Hutchinson et al (1997)[121] but this was in relation especially to HIV+ drug users. In Aberdeen, a small study (Mackenzie 1999)[122] found those infected through

injecting drug use had fallen as a proportion of the HIV+ population in the seven years, in spite of a large increase in the number of injecting drug users in the region. Heterosexual transmission and cases from overseas (in part Africa) were an increasing proportion. In this study in 55% (32/58) of AIDS related deaths the cause was pneumonia. The method was casenote review, so cause of death reporting cannot be compared with linkage studies which used ICD coding. Median survival time with AIDS was 17 months, but not all were on HAART.

McDonald et al (2009)[123] showed IDU transmission was associated with hepatitis C (HCV) infection in HIV+ people, and HCV was strongly associated with IDU. McDonald et al probabilistically linked Scottish national HIV and HCV registration databases with deaths registration data using predetermined thresholds for good matches, and extracting underlying causes of death. They found all cause mortality rates for HCV and HIV co-infection were higher than for HCV infection alone. SMRs were 5.5 and 33.8 respectively, $p<0.001$, adjusted for age sex and calendar year. Liver cancer and alcoholic liver diseases SMRs were higher for HCV monoinfection, but not statistically significant. They did not compare these with HIV monoinfection. In a not dissimilar linkage study, Palmateer et al (2007)[124] demonstrated that while registered AIDS cases annual deaths fell from 1995 to 2005, numbers of deaths with HCV as an underlying or contributing cause rose by roughly half as much as the drop in numbers of registered AIDS cases. Only ten deaths had both AIDS and HCV as causes. Frischer et al in 1997[125] (using data linkage) showed ten years earlier that HIV+ IDUs in Glasgow (1982-1994) had worse survival time and mortality than HIV- IDUs, with a substantial proportion dying from overdoses rather than AIDS.

Therefore, the survival trends in Scotland appeared to mirror those elsewhere in the developed world, however there was no recent confirmation of this in Scotland, a gap in knowledge which the current study needed to fill. There was a particular issue around both hepatitis in association with IDU, and alcohol use in Scotland, both comorbidities tended to increase mortality in this HIV+ group.

3. Aims and Objectives

Overall aim of research question

The research aimed to carry out survival, mortality and life expectancy analyses using data for a national cohort of HIV+ people in Scotland.

Specific objectives of research question

Review literature on survival, mortality, life expectancy, and demographic trends in people living with HIV in developed countries.

In this HPS Scottish cohort:

- describe frequencies and demographic trends for HIV+ in Scotland for four periods comparing alive and dead diagnosed in each era, by age group, sex, ethnicity, transmission group,
- both overall and for selected causes of death, report:
    - mortality, survival time and life expectancy from new HIV case report (diagnosis),
    - adjusted odds ratios for death for HAART era of first report, age groups, sex, transmission category, ethnic group, earliest CD4 group, and whether infected inside or outside Scotland.

4. Methods

4.1 Data access

Health Protection Scotland (HPS) was established by the Scottish Government in 2005 to strengthen and co-ordinate health protection in Scotland.[126] It covered a range of areas including environmental health, travel health, and various different classes of infection, including blood borne and sexually transmitted, which includes HIV. A national database about HIV was set up by a forerunner of HPS in 1981 as a surveillance tool to monitor the trends in incidence, prevalence and outcomes for HIV infection in Scotland.

The HPS HIV database ascertained deaths using multiple methods:

- GROS Data linkage

  Data linkage with GROS death records was first carried out for the HPS HIV database in 1993. This first linkage exercise provided information on several hundred deaths previously unreported on the HPS HIV database.

- Laboratory reports

  Although there had been no formal linkage in the last five years, this was not a concern, as HPS had from that time sought out deaths information through the dedicated HPS clerical staff located in laboratories through out Scotland. Another formal linkage was planned for later in 2010.

- Monthly extracts of death certificates from GROS

  The General Registry Office (Scotland) GROS sent on an ongoing basis to HPS a monthly extract of death certificates with any HIV code. HPS then entered the cause of death.

- Clinician reports

  Finally, clinicians carried out ongoing registration of AIDS cases and HIV deaths which had not progressed to AIDS, using a dedicated form. No cause of death information was provided through this route.

All cases in the database were known to be HIV+, even though HIV was not always recorded on the death certificate, because HPS had had all the patients tested for HIV, and all were HIV+.

Anonymised data from this HIV database was extracted by HPS on 25/9/2009 to allow investigation of the research questions. HPS initially provided the data to the researchers in two files. The first contained identifiers and up six causes of death. The second file contained identifiers and clinical surveillance information.[127] The datafields supplied are given in appendix 4. These two datasets were merged using common reference numbers.

4.2 Data linkage

Probabilistic data matching was used for this study,[128] because the two datasets had no common key on which merge cases. It was necessary for GROS to use other fields to link HPS cases with GROS cases for which mortality data was available. The HPS fields used were Gender, Date of Birth, Initials/Soundex, Postcode district of residence. The Soundex code was a method of coding surnames, using the same codes for the same sounds to improve matching.[129] Probabilistic data matching was described by Newcombe[130] who first used it in the early 1960's. It used the cumulative accuracy of a number of variables to match. Probabilistic was contrasted with deterministic matching, which looked for an exact match between one or more variables in the records. In a US example, probability matching linked National Health Interview Survey data with the National Death Index.[131]

There was a receiver-operating curve in probabilistic matching, where as with any screening process there was a trade off between sensitivity and specificity. Sensitivity was defined by Hennekens[132] as 'the probability of screening positive if the disease is truly present' (cases found divided by all cases) and specificity was 'the probability of testing negative if the disease is truly absent' (non cases found divided by all non cases). According to a high quality systematic review using Cochrane methodology, probabilistic data linkage in health databases had around 99-100% specificity and 74%-98% sensitivity.[133] Likewise, the sensitivity in the current study was lower than the specificity but higher than would have been the case in deterministic matching.

Some patients recorded as not deceased may have been deceased but lost to follow up, for example having moved. To check the potential impact of this the proportion of patients not known to be deceased but with no service appointment recorded in the last 5 years was compared with those known deceased on age and sex using chi square. If those not seen in the last five years were demographically similar to the known deceased, that was evidence in support of the representativeness of the known deceased in relation to all potentially deceased.

4.3 Death certification processes and cause of death data

The cause of death data acquired through the linkage was collected by GROS from death certificates. It was a legal requirement that a medical certificate of death (see appendix 2) be completed for all deaths in the UK by a registered medical practitioner. There was potential for inaccuracy, both in death certificate completion (for example doctor error), at the coding stage, (for example coder error) and at the data linkage stage (if using probability matching). Coding was automated in Scotland from 1996. There was no gold standard to measure accuracy, but manual and automated coding agreed in 89% of cases in a 1995 audit by GROS.[134] The linked data did not distinguish between English/Welsh/Northern Irish and Scottish registered deaths. There was no distinction between direct (first listed) or antecedent causes (positions 2-4 in Scotland, 2-3 in England, including underlying cause, which was the last cause in this first group). There was no distinction of associated conditions (final three conditions (England) or final two conditions (Scotland)). For the current study identification of underlying cause was reliant to some extent on the judgement of an experienced health researcher, using ICD9 and ICD10 coding system guidance. To increase validity a random audit was carried out of the researcher coding of primary (underlying) cause by CJ, a registered medical practitioner with clinical experience in the HIV setting. This is the technique used to quality assure medical coders within the NHS.

A copy of the current medical certificate of death used in Scotland can be found in Appendix 2.

Cause of death data was coded using the International classification of diseases (ICD) system. Owing to the span of the time period over which data had been collected, deaths had been coded using the ICD, 9th and 10th revisions.

4.4 Coding procedure and Data preparation

Descriptions relating to the individual cause of death codes supplied were obtained from GROS and HPS. Codes were linked to their descriptions using a lookup table of ICD9-CM[135] and ICD10 descriptions. HPS advice was taken in this process. Further information is in appendix 9.

Primary cause of death

Other studies did not use the term 'primary cause of death'. They used either 'underlying cause'[136-138] or 'any cause',[139;140] or did not clearly specify their approach, e.g. ART-CC which included 'both definitive and presumptive diagnoses'[141] and Long.[142]

For this study, 'primary cause' was a concept not captured by the idea of 'direct cause' (death certificate guidance in Scotland stated this was in the first of the six positions on the death certificate) or 'underlying cause' (the last of the antecedent causes, therefore the start of the causal chain leading to the direct cause). The linked death code data did not distinguish between the first four and later positions, so the underlying cause was not identifiable by position.

Cause of death coding

The primary cause of death was identified from all six code positions using rules described further in appendix 9. To code the diagnostic groups, the lists of ICD9 and ICD10 codes and descriptions were assigned one of 31 groups for analysis (ICD9 first). The face validity of the groupings was checked with a medical practitioner (CJ). Codes in all six positions were recoded to the relevant group for each death. The primary cause of death was also recoded. AIDS coding the Centre for Disease Control definition[11] was used to decide which diagnoses were AIDS defining, and this was additionally interpreted through medical practitioner input (CJ). Hepatitis was

coded for hepatitis B, C or any. Further details of coding procedures are given in appendix 9.

To merge the deaths data with the treatment data, the translated death codes data was used as a lookup table using case reference number as the key. The single file resulting contained both treatment and deaths data. As an audit trail of the methods used for translation the translation spreadsheet was retained.

Ethnic groups recoding.

In the original data ethnic groups were subdivided within the Asian, Black and White groups. These were analysed as three broad groups and then two groups, (white and non-white) to allow for analysis of small numbers. This approach has been used in other studies, a search on the term 'non-white' in Ovid records from 2006 produced 406 records 26 of which were in the context of HIV or AIDS, for example, one referred to ethnic minority men as 'non-white' men.[143]

Age group coding

UK Census age groups were used for greater consistency with wider datasets. The lower and upper end categories had to be merged for some analyses (e.g. chi-square, see below) as shown in the list below:

0-15	16-19	20-24	25-34	35-44	45-64	65-74	75+
0-15	16-19	20-24	25-34	35-44	45-64	65+	
0-19	20-24	25-34	35-44	45+			

Risk group coding

Higher level risk groups coding was retained as given in the original data. Heterosexual risk group subcategories were combined to create three broad groups, Abroad, UK with no evidence of high risk partner (HRP), and HRP (UK).

4.5 Data analysis

Date calculation (for example subtracting dates to determine periods of time for survival analyses, and age at first report) was carried out in SPSS to the nearest day or to fractions (to two decimal places) of a year.

Statistical analyses

Missing data was generally excluded from analyses of proportions, but noted. Where a substantive response of 'unknown' (e.g. unknown transmission) had been given, this was not treated as missing but as a category in its own right. Data was generally not reported in groups of less than 10 to protect individual identities. Where a group of less than 10 would otherwise occur, the number was replaced by a single asterisk.

Chi square (χ^2) and Chi square for trend

Pearson chi square and chi-square for trend were used for descriptive analysis of the data. Analysis used Chi square only when data met the test assumptions. Test assumptions for Pearson Chi square required that the expected frequencies for each category should be at least 1. No more than 20% of the categories should have expected frequencies of less than 5.[144] Where Chi square for trend was used it was stated.

Kendall's tau and Spearman's rho were other appropriate tests used for testing the statistical significance of changes by HAART era for age at first report. As the table had differing numbers of rows and columns, tau-c (which ignores ties) was used rather than tau-b (which corrects for ties).

4.6 Mortality method

Annual mortality rates

Mortality rate was a measure of incidence.[145] Annual Mortality rate per 1000 was calculated for each year in the period 1981-2008, adjusting for the changing caseload during the year. Mortality rates were calculated in Microsoft Excel (2003) by using the standard equation:

$$\frac{\text{(total deaths each year)}}{\text{(deaths and live cases at mid year)}} * 1000$$

The average of these rates was taken for each of the HAART eras.

Standardisation

Differing age structures could mean crude rates did not give a valid comparison of two or more populations. Standardisation of rates allowed a valid comparison adjusting for different demographic structures in each group, meaning for example mortality or morbidity trends owing to other factors could be distinguished from the effects of changing age and sex make up. In direct standardisation the study population(s) were standardised to an external reference population, in indirect standardisation subgroup(s) of the larger population were compared to the larger population, which is used as the reference population.

An indirectly age standardised mortality ratio was calculated for males and females separately.

SMR = (Observed deaths/expected deaths) X 100

Expected deaths were calculated by multiplying the observed population in each age group by the death rate for that group in the reference population (see below for the reference populations used).

The SMR is an abstraction, showing how likely there are to be deaths in the population in comparison to the reference population, adjusting for the different age structures. The multiplication by 100 helps understanding: if SMR is 100 then expected and actual deaths are the same, so the SMR compares the death rate in the population of interest as a percentage of deaths which would be expected given the rate in the reference population.

Confidence intervals for SMRs were calculable using the formula:[146;147]

$$SMR \pm 1.96 * ese(SMR), \text{ where } ese(SMR) = 100 * \frac{\sqrt{Observed}}{Expected}$$

Finally, an overall calculation was carried out to express the mortality as a crude rate per 1000 person years in the study. Person years were calculated for each individual as time from first report to death or censored in SPSS, and were allocated to age ranges at death or censored.

This was not the classical situation for standardisation of mortality rates. Classically, known age/sex rates in one year are applied to the population by age and sex groups in one other year to derive expected rates for the calculation of observed/expected rates*100 (SMR) for the second year.

Therefore, two methods were used. The first was to derive the prevalent population for a mid-point date in each era by selecting those who were referred before the date in question, and were still alive at that date.

Dates used were:
1. 30.6.1989
2. 30.6.1998
3. 30.6.2001
4. 30.6.2004
5. 30.6.2007

The first point (30.6.89) was the reference population for the indirect standardisation. Age groups were allocated using age calculated in SPSS at each reference date (0-19, 20-39 and 40+). For those who died in the three year period centring on each reference date, age at death was calculated and grouped by selecting deaths in the period in question and calculating DOB-DOD. The deaths in that year and the preceding and following years were then used to calculate age/sex specific mortality rates (deaths divided by live cases for each age and sex group).

A cross tabulation of age group by sex for those selected as referred by each time point and who had not died by then, gave the prevalent populations to enable expected deaths to be worked out. A similar cross tabulation of those selected as having died in the three years spanning each time period gave the actual deaths.
The age/sex mortality rates were applied to the prevalent population at times 2, 3, 4 and 5 and summed to give expected deaths at points 2, 3, 4 and 5.[145] Age groups were allocated afresh for the prevalent population using age calculated at each succeeding time point to adjust for differing age structures (see syntax in appendix

10). Then the indirectly standardised mortality ratio was calculated for all points using point 1 as the reference population, and the methods described above.

Secondly, indirect standardisation using the general Scottish population death rates for 2001 was carried out. It was appropriate to use the whole of Scotland as the HPS dataset covers the whole of Scotland. A quick search of Medline 1996-2009 using terms HIV, Scotland and (deprivation, or socio or SIMD or Carstairs) produced no relevant papers. The lack of evidence suggested it was appropriate to use the whole Scottish population, rather than a particular deprivation subgroup, as the reference population. The mid 2001 population estimate was the most likely to be accurate as closest to the census date of 29 April 2001. It was at an approximate midpoint in the post HAART period, within the HAART era rather than early HAART or 'ultra-active' HAART. GROS had revised earlier estimates available for 1982-2000 to be in line with the 2001 census. Observed and actual cases were then summed for all age ranges and used to calculate an overall ratio.[145]

4.7 Logistic regression method

Unadjusted odds ratios were calculated for various individual factors by HAART era in SPSS using cross tabulation, but cannot allow for more than one factor in modelling the relationship between independent and dependent variables, factor and outcome. Binomial logistic regression can adjust for more than one factor.[148] SPSS v 17 was used to carry out logistic regression to adjust for risk factors (transmission method), age structures, sex composition, ethnicity etc across HAART eras, to see whether the adjusted risk of death (OR) was different to unadjusted.

Statistical advice indicated that it would be inappropriate to use logistic regression unless deaths data was within a clearly defined period of time the same for each individual. Five year survival was considered, but rejected in favour of firstly adjusting for time after first report to death or censored in all the logistic regression equations.

For survival analysis, a different method was needed (see below) since logistic regression could not make full use of survival time for censored cases who did not survive for the full period but did survive for a part of it.

4.8 Survival time analysis method

Kaplan Meier analysis of survival across eras was carried out in SPSS. Kaplan Meier can deal with censored observations for which the actual survival time is not known, and is not based on assumptions of normality. The log rank test[149] was used to assess whether the survival times between groups were different at a statistically significant level. Hazard ratios were calculated using Cox's proportional hazards model for the regression, and adjusting for one covariate only. That tested the null hypothesis of 'equal hazards' for two groups. Cox's had the additional capability, to Kaplan Meier, of including multiple covariates and continuous covariates in the regression model, but since that was done in binomial regression it would have been over-analysis to do it again. The hazard rate described the risk of death for a particular short time interval, or more precisely the 'conditional instantaneous event rate calculated as a function of time'.[150] The hazard ratio compared the hazard rates between groups. The difference in the log of hazards for each covariate category, and its statistical significance, were generated in SPSS. Log minus log plots were used to assess whether the proportional hazards model was applicable to the data.

The survival time analysis was used to assess differences in survival time for demographic groups between eras.

4.9 Life expectancy – Life table method

A life table remained the only method of estimating mean life expectancy at a particular survival time. Life tables were one of the first public health techniques, an early example of their use is by John Graunt, in 1662.[151]

A current complete life table was created for life expectancy at first confirmed report of HIV. 'Complete' refers to the use of one year survival intervals in contrast to an 'abridged life table' which uses another length of interval, typically five years.[151]
'Current' refers to the use of present day observed mortality.[151]

The approach described by Selvin[151] was used. For 2008, L_x the cumulative years lived by the entire cohort between ages x and x+1 was calculated using SPSS. Then

T_x, the total time lived by all individuals beyond age x, and $e_{x,}$ mean years of remaining life (life expectancy) at age x were calculated. The method was to calculate L_i starting with the first, by deducting the events during each interval from the number entering the interval, and adding half (or other appropriate percentage) of the deaths back again. The final T_i (cumulative years after first report) for those 27 years from first report is equal to L_i (time lived by individuals) from 27 years from first report. The 27th year was the last year of survival available. Then, working from the bottom of the table up L_i was added to T_i to get the next T_i. The final step was the calculation of e_x (life expectancy) at age x. Where l_x = number of individuals at risk at exactly age x:

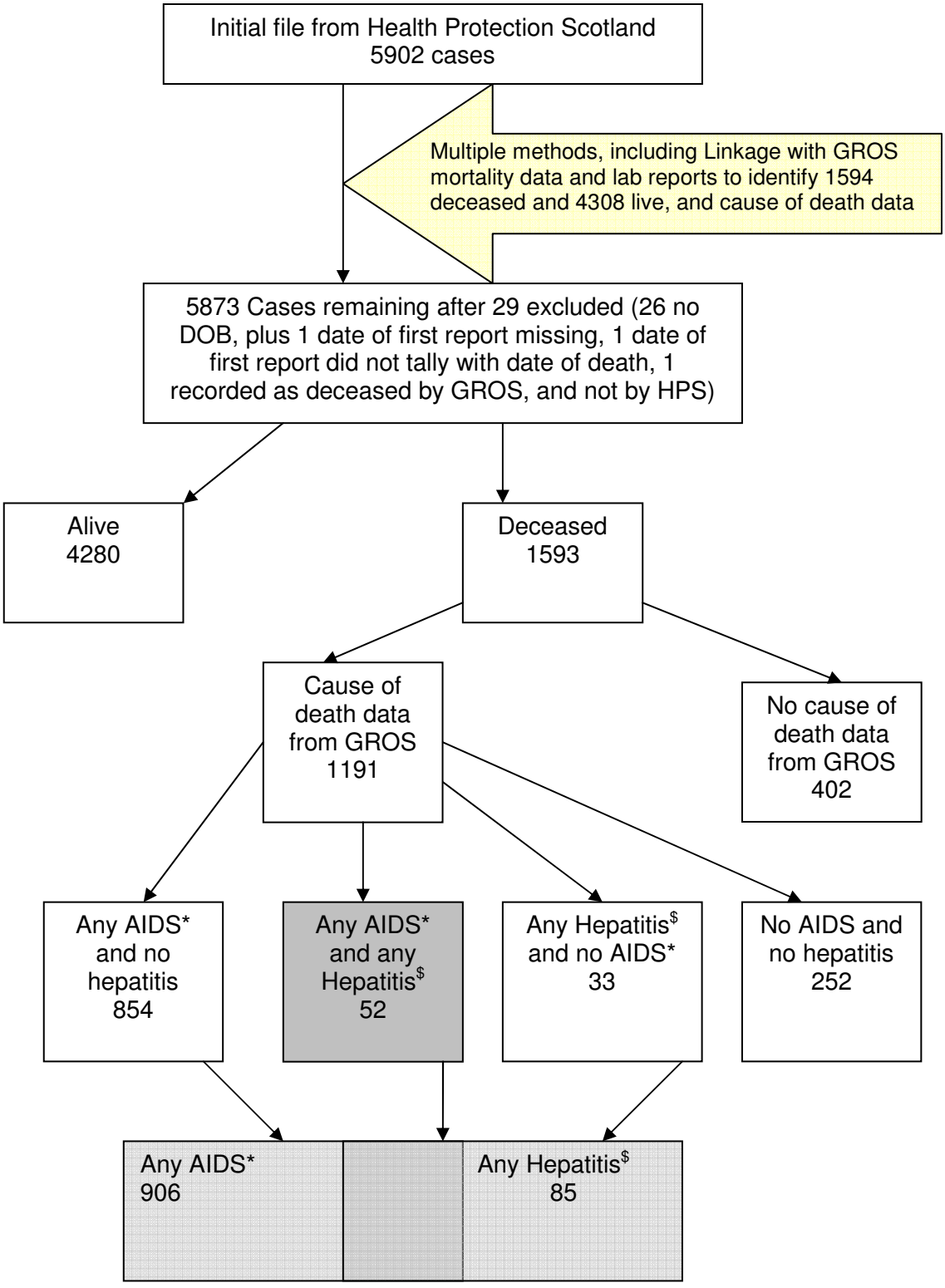
$$e_x = \frac{T_x}{l_x}$$

In this case the proportion of deaths added back for L_x was 0.5, since the start date was date of first report, not date of birth[152].

A current and complete lifetable is derived from "present day observed mortality (current) and applied to one-year age intervals (complete)." To achieve this, only those either alive or who died in 2008 were included. The censor date was 31.12.2008. Those who died in 2009 were included if they became patients on or before 31.12.2008. The survival time used for the 2008 current complete lifetable was therefore time from HIV initial first report to death or when censored at 31.12.2008. This table was stratified by age at first report (using the SPSS command 'splitfile' and organising output by age groups).

Prediction of life expectancy at older ages was possible by creating a current complete life table for 2008 by single year of age (rather than for years after diagnosis as before) and again carrying out a further analysis stratifying this by age group at first report to confirm whether or not that made a difference to life expectancy.

4.10 Case flow diagram



*Any AIDS = any AIDS defining diagnosis as any cause of death
$Any Hepatitis =Any Hepatitis B or C diagnosis as any cause of death

4.11 Ethical issues

There was no named data, but because certain fields (for example ethnicity, sex and age) were included that might potentially enable someone to work out the identity of an individual, and because it was patient data, the eight principles of the Data Protection Act (1998) applied.[153] Therefore research ethics approval for the project was sought and obtained from the University of Glasgow. Consent was given by the HPS lead consultant. For confidentiality reasons numbers below 10 were not reported. To further ensure no living individual could be identified the data was kept in electronic form on a password protected computer.

The issues of consent and information provision were of concern in this vulnerable population. There were no other risks of harm arising from the project to the research subjects, since all the data was already collected. Subjects were not contacted. At the time of original data collection they had been provided with an information leaflet about the data being collected, stating the information might be used in research, and had consented to this.

A copy of the approval letter from the ethics committee (no amendments were required at initial submission) is included at appendix 5.

The initial understanding was that the HPS data did not include children but when received it did contain a small number of children (43 were under 16 years old as at the date of data extraction (25/9/09). When this was realised, Ethical Approval was sought and given to include data on under 16s in the analysis. The letter granting approval to the amendment is included in appendix 5.

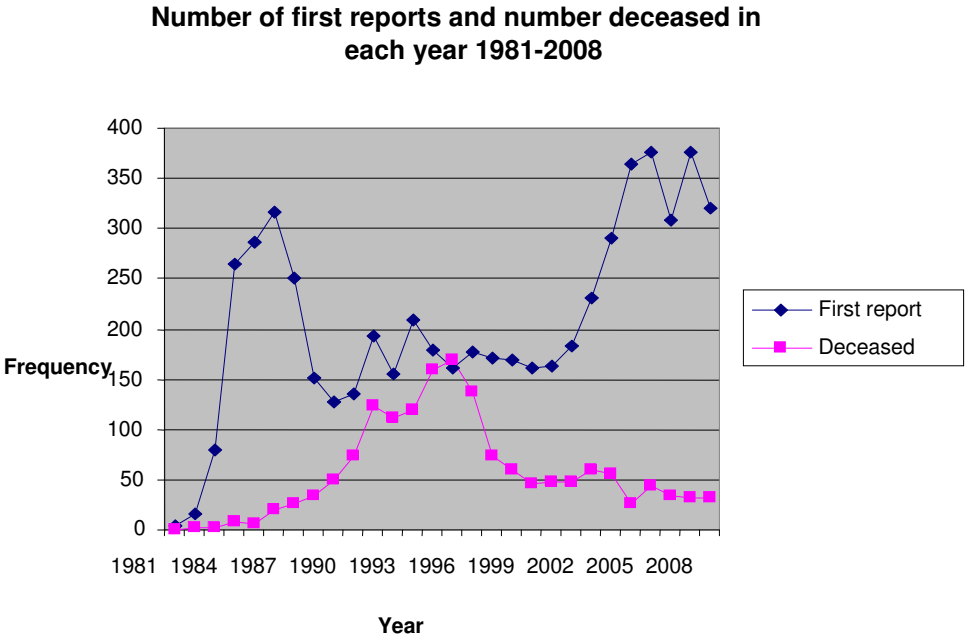
5. Demographic analysis

This chapter aims to describe the data provided about people testing positive for HIV in Scotland. It is structured in four main sections: Age, Sex, Ethnicity, and Transmission group. Each of these has two subsections, these are:

1. descriptive statistics as appropriate by whether alive or deceased,
2. trends by era.[a]

Figure 5.1 (below) gives an overview of deaths and new cases since 1981.

Fig. 5.1 mortality and first report trends in HPS dataset.[b]



A number of patients had not had an appointment at the service within the five years before death or the date of data extraction. To explore the likelihood of systematic error (bias) arising from underestimation of the deceased numbers, chi square tests were done for sex, age group and risk group to see if there was a statistically significant difference between those who had and had not attended in the five years prior to death or censoring. For sex, $p<0.64$, for age group, $p<0.001$, and for risk group, $p<0.11$. Those aged 25-34 were less likely to have an attendance in the last 5

[a] For demographic groups by era of first report and whether alive or deceased at 25.9.09 see appendix 11

[b] 'first report' means first report in Scotland, and was more accurate than 'diagnosis' here, as patients may have been diagnosed previously elsewhere

years, although the effect was not large. Patients with missing and invalid dates of last attendance were excluded.

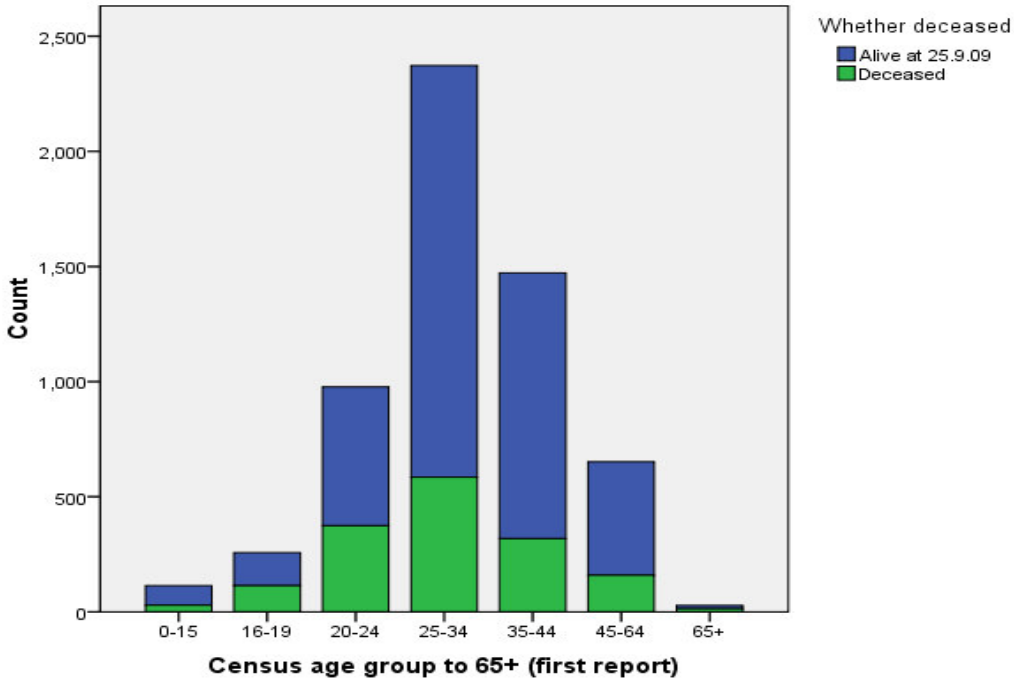
In the current study, of the 1594 deaths identified, 1193 (a sensitivity of 74.84%) were matched on cause of death (COD). As further validation, the deaths not matched on COD were included in analyses where possible, to ensure they were not significantly different from the matched death cases. In the following analyses the dataset of 5873 (1593 deceased and 4280 live) is used (i.e. the number after exclusions – as per case flow diagram (see methods).

5.1 Age

Age demographics

The mean age at first report overall was 32.1 (SD 10.2). The mean age at initial consultation (first report) for those still alive was 32.6 years (95% CI 32.3-32.9, SD 9.9) and for those deceased, the mean age at first report was 30.8 years (95% CI 30.3-31.4, SD 10.9).

Fig. 5.2: Whether deceased at 25/09/09 by census age group at HIV initial confirmed first report



An independent samples t-test comparing age at first report for all the live and all the deceased gave a significant result (p<0.001). Within each HAART era, the t-test gave results in table 5.1.

Table 5.1 Differences in mean age at first report between live and deceased Scottish patients with an HIV diagnosis within four eras of HAART.

HAART era of first report	Mean age: Live (N)	SD (live)	Mean age: Deceased (N)	SD (Deceased)	Mean age difference and CI	Statistical significance (P)*
Pre HAART	28.2 (1261)	8.6	29.6 (1417)	10.1	1.4(2.1-0.7)	**<0.001**
Early HAART	33.1 (430)	9.4	38.4 (71)	9.8	5.3 (7.7-2.9)	**<0.001**
Late HAART	33.8 (810)	9.5	41.6 (58)	13.5	7.7 (10.3-5.1)	**<0.001**
Ultra Active HAART	**35.1 (1779)**	**10.1**	**42.1 (47)**	**14.0**	**7.1 (10.0-4.1)**	**<0.001**

* Equal variances not assumed

Table 5.1 was convincing evidence against the null hypothesis that there was no difference in age at first report between those who died before 25.09.09 and those still alive at that date. This applied for those reporting in each era separately.

All cases were analysed by census age groups of age at first report. First report of HIV was most frequent in those aged 25-34 and 35-44 years at first report.

Changes by HAART era for age at first report

The chi square for trend was significant for proportions in each census age group at first report in each HAART era (Table 5.2).

Table 5.2 Age group at first report by HAART era of first report

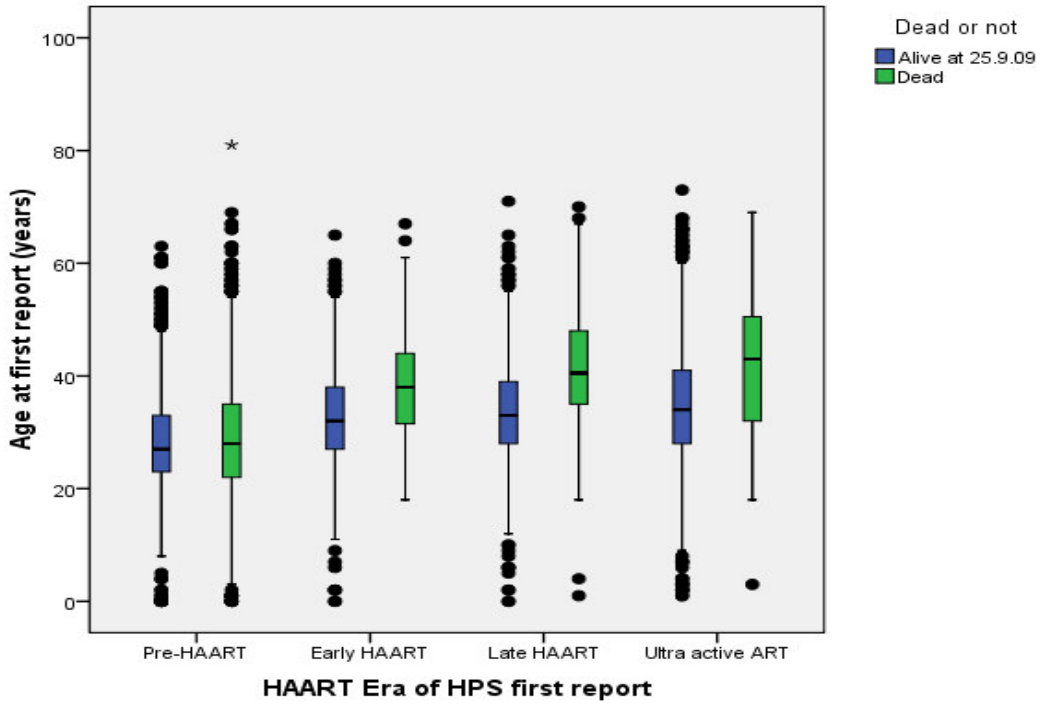
Census age group to 45+	Pre-HAART n(%)	Early HAART n(%)	Late HAART n(%)	Ultra active ART n(%)	Total N(%)
0-15	62 (2)	10 (2)	17 (2)	25 (1)	**114 (2)**
16-19	206 (8)	10 (2)	15 (2)	26 (1)	**257 (4)**
20-24	664 (25)	41 (8)	93 (11)	179 (10)	**977 (17)**
25-34	1125 (42)	224 (45)	346 (40)	678 (37)	**2373 (40)**
35-44	447 (17)	155 (31)	268 (31)	602 (33)	**1472 (25)**
45+	174 (7)	61 (12)	129 (15)	316 (17)	**680 (12)**
Total N (%)	**2680 (100)**	**501 (100)**	**868 (100)**	**1826 (100)**	**5873 (100)**

The proportions of total patients increased with HAART era in older age groups (p<0.001). The shift was most evident from pre-HAART to early HAART. Kendall's tau c was highly significant but showed a weak to moderate correlation (tau c = 0.234, p<0.001)[c]. Spearman's rho, another measure of ordinal correlation was similar (rho = 0.294, p<0.001). The high significance levels result from the large sample, but the size of effect was not large.

The lowest census age groups were re-grouped to a 0-19 age group. The χ^2 for trend statistics were statistically significant for the live and deceased groups separately at p<0.001. The non parametric statistics were:
Live: Kendall's tau-c: 0.224, p<0.001, Spearman's rho: 0.279, p<0.001
Deceased: Kendall's tau-c: 0.133, p<0.001, Spearman's rho: 0.285, p<0.001

This gave convincing evidence against a null hypothesis of no association between age at first report and HAART era of first report. Fig. 5.3 shows how median age (shown by the cross bar within each box) at first report increased for both live and deceased patients.

Fig. 5.3 Boxplot by age at first report by HAART era of first report



[c] Tau c can vary between -1 (no association) and +1 (strong association), but the extremes (-1 and +1) can be obtained only from square tables (SPSS help system).

In summary, mean age at first report increased with HAART era for both live and deceased cases and mean age was higher for deceased cases than for live cases for all four eras.

Mean age of patients still alive

Mean ages for the prevalent (live) patients were compared between the sexes at 30 June in five selected years at approximately the mid point in each era plus a latest point, (Table 5.3). This was not age at first report. These means were calculated by selecting the prevalent patients and calculating their age at each of the time points.

Table 5.3 Mean age (years) at 30 June in each year of prevalent patients**

Sex/year	1989	1998	2001	2004	2007	30.3.2009
female	27.83	34.51	36.67	37.29	38.27	**39.03**
male	29.95	37.39	39.45	41.44	42.78	**43.43**
overall	29.36	36.60	38.69	40.19	41.43	**42.09**
Number referred by 30.6 and not died by 30.6 in year of column	**1194**	**1613**	**1944**	**2549**	**3573**	**4280**

**latest is 30.3.2009

There was a statistically significant difference in mean age as shown by independent samples t-tests ($p<0.001$) between the sexes for the prevalent (live) patients at each time point. Because of the way the means were calculated it was not possible to carry out χ^2 for trend over the time points in SPSS. Mean age increased with time point both for each sex and overall. The mean age of people living with HIV in Scotland was increasing.

5.2 Sex

Sex demographics

Table 5.4 Sex by whether deceased at 25/09/09

	Alive (%)	Deceased (%)	Total (%)
Female	1304 (80.3)	320 (19.7)	**1624 (100)**
Male	2976 (70.0)	1273 (30.0)	**4249 (100)**
Total	**4280 (72.9)**	**1593 (27.1)**	**5873**

Nearly three quarters of the cases overall were male (72.3%). As table 5.3 shows, the proportion of men who were deceased was 30%, which was greater than the

proportion of women who were deceased, which was 20%. χ^2 comparing proportions deceased between sexes was statistically significant, p<0.001).

Age group at first report was associated with sex (Table 5.5 and Table 5.6). For both live and deceased χ^2 was statistically significant, (p<0.001). Men were more likely to be older than women at first report. Chi square for trend for age group by sex was statistically significant, (p<0.001) for both live and deceased patients.

Table 5.5 Sex by age band for deceased

	Census age group to 65+ (first report) (Deceased)						Total(%)
	0-15(%)	16-19(%)	20-24(%)	25-34(%)	35-44(%)	45+(%)	
Female	9 (2.81)	39(12.19)	102(31.88)	116(36.25)	36(11.25)	18(5.63)	**320(100)**
Male	20(1.57)	75(5.89)	272(21.37)	469(36.84)	282(22.15)	155(12.17)	**1273(100)**
All	**29(1.82)**	**114(7.16)**	**374(23.48)**	**585(36.72)**	**318(19.96)**	**173(10.86)**	**1593(100)**

Table 5.6 Sex by age band for live

	Census age group to 65+ (first report) (Alive at 25.9.09)						Total(%)
	0-15(%)	16-19(%)	20-24(%)	25-34(%)	35-44(%)	45+(%)	
Female	32(2.45)	60(4.6)	249(19.1)	619(47.47)	262(20.09)	82(6.29)	**1304(100)**
Male	53(1.78)	83(2.79)	354(11.9)	1169(39.28)	892(29.97)	425(14.26)	**2976(100)**
All	**85(1.99)**	**143(3.34)**	**603(14.09)**	**1788(41.78)**	**1154(26.96)**	**507(11.85)**	**4280(100)**

Age by sex

Overall, mean female age at first report was 29.4 years (95% CI 28.9-29.9, SD 9.5), mean male age was 33.2 (95% CI 32.9-33.5, SD 10.3), giving convincing evidence against a null hypothesis of no difference in mean age between patients of each sex. An independent samples t-test between males and females for mean age at first report was highly statistically significant (p<0.001) for both live and deceased patients separately.

Changes by HAART era for sex

For sex, χ^2 for trend overall was statistically significant (p<0.001), with a trend towards a greater proportion of women and a lower proportion of men diagnosed, over time (Table 5.7). Chi square for trend gave sufficient evidence to reject a null hypothesis of no linear trend in relative proportions of men and women diagnosed (suggesting there was a trend).

This trend was assessed separately for the patients alive at 25.09.09 and those deceased at that date (Table 5.7):

Table 5.7 proportions of each sex, split by whether alive or deceased

	Sex	Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra active ART (%)	Total N(%)	P for χ^2 for trend
Alive	Male	913 (72.4)	320 (74.4)	536 (66.2)	1207 (67.8)	**2976 (69.5)**	
	Female	348 (27.6)	110 (25.6)	274 (33.8)	572 (32.2)	**1304 (30.5)**	
	Total (N)	**1261 (100)**	**430 (100)**	**810 (100)**	**1779 (100)**	**4280 (100)**	**<0.001**
Deceased	Male	1127 (79.5)	61 (85.9)	46 (79.3)	39 (83)	**1273 (79.9)**	
	Female	290 (20.5)	10 (14.1)	12 (20.7)	8 (17)	**320 (20.1)**	
	Total (N)	**1417 (100)**	**71 (100)**	**58 (100)**	**47 (100)**	**1593 (100)**	**<0.443**
Overall	Female	638 (23.8)	120 (24)	286 (32.9)	580 (31.8)	**1624 (27.7)**	
	Male	2040 (76.2)	381 (76)	582 (67.1)	1246 (68.2)	**4249 (72.3)**	
Overall total		**2678 (100)**	**501 (100)**	**868 (100)**	**1826 (100)**	**5873 (100)**	**<0.001**

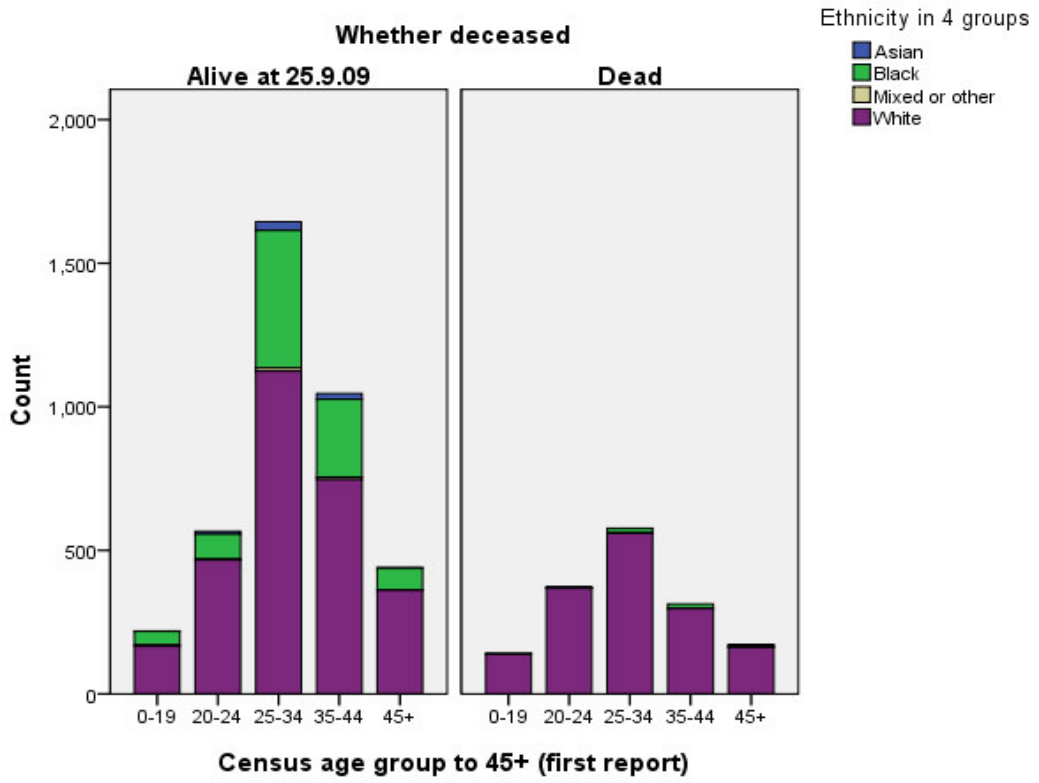
The proportion of live patients who were male decreased ($p<0.001$). So there was evidence that (in those still alive) there was a trend of a decreasing proportion of males. There was an overall decrease in the number of deaths.

5.3 Ethnicity

Ethnicity demographics

For ethnicity (Fig. 5.4), data was missing or recorded as no information in 381 cases, which were excluded from further analysis of ethnicity. Ethnic categories were re-grouped to four from the original thirteen. Of the remaining 5492 cases by far the largest ethnic group was white (80%), and next was black (18%). The mixed race patients were youngest, on average at first report, but numbers were small.

Fig. 5.4: Whether deceased at 25/09/09 by census age group at confirmed first report of HIV and ethnic group



The sex balance varied by ethnic group, with the highest proportion of women in the black group (χ^2 p<0.001) (table 5.8).

Table 5.8 Ethnicity frequencies and sex at first report

Ethnic group	Female n (%)	Male n (%)	Total N (%)	
White	874 (19.9)	3514 (80.1)	**4388 (100)**	**χ^2<0.001**
Black	604 (60.5)	394 (39.5)	**998 (100)**	
Asian	35 (50)	35 (50)	**70 (100)**	
Mixed or other	11 (30.6)	25 (69.4)	**36 (100)**	
Total	**1524 (27.7)**	**3968 (72.3)**	**5492 (100)**	

Mean age at first report was highest for Asian people (table 5.9).

Table 5.9 Ethnicity frequencies and mean age at first report

Ethnic group	Mean Age at first report (years)	SD for mean age re-grouped ethnic groups	N	Percent
White	31.85	10.393	4388	**79.9%**
Black	32.24	9.273	998	**18.2%**
Asian	33.03	8.917	70	**1.3%**
Mixed or other	29.47	13.708	36	**.7%**
Total	**31.92**	**10.207**	**5492**	**100.0%**

χ^2 was statistically significant for the association between ethnic group and death,. The most likely to be deceased were white and mixed ethnic groups (table 5.10).

Table 5.10 Re-grouped ethnic group by whether alive or deceased at 25.9.09

Re-grouped ethnic group	Alive n(%)	Deceased n(%)	Total (100%)	
White	2864 (65.3)	1524 (34.7)	**4388**	χ^2<0.001
Black	957 (95.9)	41 (4.1)	**998**	
Asian	65 (92.9)	*	*	
Mixed or Other	30 (83.3)	*	**36**	
Total	**3943 (71.3)**	**1577 (28.7)**	**5492**	

Changes by HAART era for ethnicity

Changes in proportions of each ethnic group diagnosed in each era are set out in Table 5.11. Apart from the mixed/other group (too small) each ethnic group was compared against all of the others combined to give a clear chi square for trend for that group. However all results are presented in a single table.

Table 5.11 Number and percentage of cases by HAART era and ethnic group

	HAART Era of HPS first report				Total	P for χ^2 for trend overall
	Pre-HAART	Early HAART	Late HAART	Ultra active ART		
White	2479	387	521	1001	**4388**	
	95.1%	83.6%	64.9%	61.8%	**79.9%**	**<0.001**
Black	114	62	256	566	**998**	
	4.4%	13.4%	31.9%	35.0%	**18.2%**	**<0.001**
Asian	*	10	14	40	**70**	
	*	2.2%	1.7%	2.5%	**1.3%**	**<0.001**
Mixed or other	*	*	12	12	**36**	
	*	*	1.5%	.7%	**.7%**	
Total	**2607**	**463**	**803**	**1619**	**5492**	
	100.0%	**100.0%**	**100.0%**	**100.0%**	**100.0%**	

The proportion of black and Asian patients having a first report of HIV in Scotland increased, that of white patients decreased. Chi squares for trend for all were statistically significant ($p<0.001$), giving convincing evidence against a null hypothesis of no trend for each of these across the HAART eras.

5.4 Transmission group

Transmission group demographics

The two most frequent transmission groups were Men who have Sex with Men (MSM), and heterosexual people, with Intravenous Drug Users (IDUs) ranking third (Tables 5.12, 5.13 and Fig 5.5). With the exception of mother to child (vertical) transmission, the youngest transmission group at first report were haemophiliac people. Excepting others and unknown, the oldest were blood/tissue transfers.

Table 5.12 gives an analysis of transmission group by sex. The highest proportion of females was among heterosexuals.

Table 5.12 Transmission group by sex

	Sex		Total (100%)
Transmission Route	**Female (%)**	**Male (%)**	
Blood/Tissue Transfers	21 (42)	29 (58)	**50**
Haemophiliac people	0	87 (100)	**87**
Heterosexual people	1127 (55.8)	893 (44.2)	**2020**
Injecting Drug Users (IDU)	407 (30.6)	924 (69.4)	**1331**
IDU and also MSM	0	51 (100)	**51**
Men who have sex with men (MSM)	0	2136 (100)	**2136**
Other	5 (35.7)	9 (64.3)	**14**
Mother to child (vertical) transmission	38 (50)	38 (50)	**76**
Unknown	26 (24.1)	82 (75.9)	**108**
Total	**1624 (27.7)**	**4249 (72.3)**	**5873**

In those who were deceased, IDU were the most numerous transmission group, with MSM and heterosexuals following. The order was different for the live, with heterosexuals most numerous and MSM and IDU following (Fig. 5.5 gives an age group breakdown).

Fig 5.5 Whether deceased at 25/09/09 by transmission group and census age band

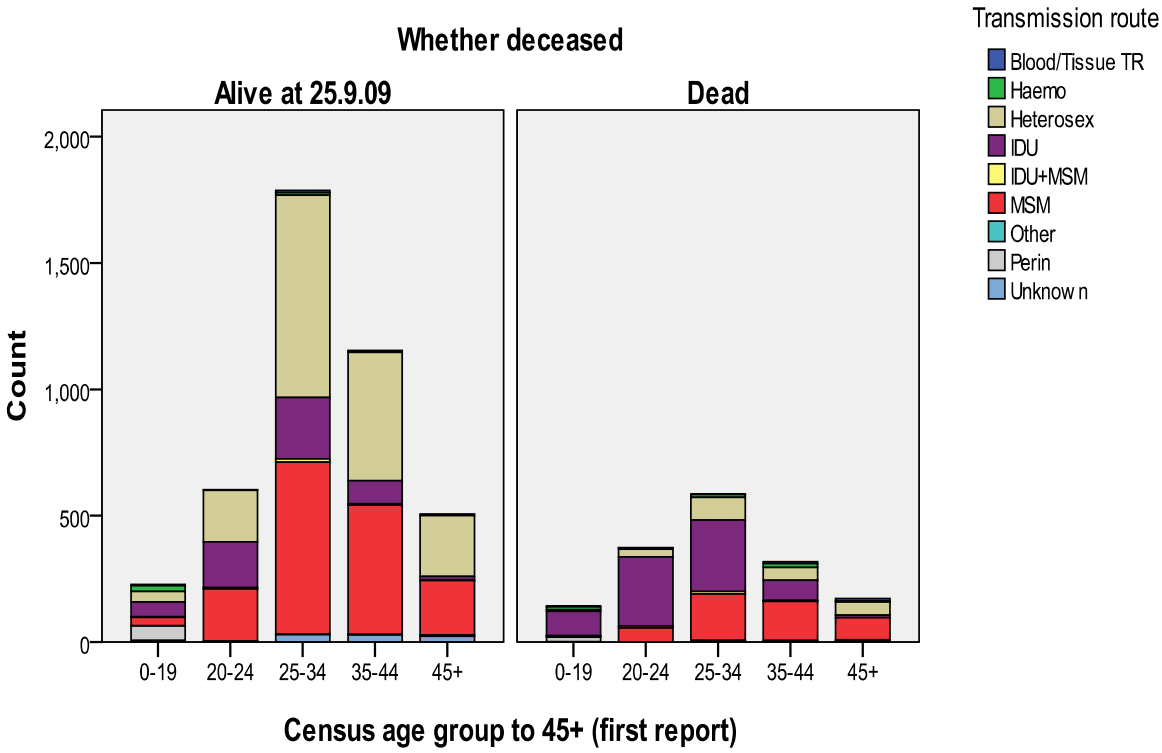


Table 5.13 Transmission group by whether alive or deceased

Transmission group	Alive n (%)	Deceased n (%)	N (%)	Overall mean age at first report (years)	Overall SD for age (years)
Others	10 (71.4)	*	**14 (0.2)**	42.6	**17.9**
Blood/Tissue Transfers	26 (52.0)	24 (48.0)	**50 (0.9)**	36.8	**17.8**
IDU and also MSM	26 (51.0)	25 (49.0)	**51 (0.9)**	28.1	**7.0**
Mother to child (vertical) transmission	58 (76.3)	18 (23.7)	**76 (1.3)**	3.6	**3.6**
Haemophiliac people	39 (44.8)	48 (55.2)	**87(1.5)**	25.4	**12.1**
Unknown cases	90 (83.3)	18 (16.7)	**108 (1.8)**	37.7	**11.8**
Injecting drug users (IDU)	589 (44.3)	742 (55.7)	**1331 (22.7)**	26.9	**7.1**
Heterosexual people	1793 (88.8)	227 (11.2)	**2020 (34.4)**	34.2	**9.6**
Men who have sex with Men (MSM)	1649 (77.2)	487 (22.8)	**2136 (36.4)**	34.4	**9.2**
Total	**4280 (72.9)**	**1593 (27.1)**	**5873 (100.0)**	**32.1**	**10.2**

Overall χ^2 for live compared to deceased, by transmission category was statistically significant, ($p<0.001$). The highest proportion of deceased was among haemophiliac people and IDUs.

If the transmission method was recorded as heterosexual, a transmission subcategory was included in the data. For those thought to have acquired HIV through heterosexual transmission, some 65% had acquired it abroad, see table 5.14:

Table 5.14 heterosexual transmission route by alive or deceased at 25.9.09

	Whether deceased		Percentage	Total (N)
Broad Hetero-transmission group	Alive n(%)	Deceased n(%)		
Exposed abroad	1222 (93.7)	82 (6.3)	64.55%	**1304**
Exposed UK, Partner	289 (83.8)	56 (16.2)	17.08%	**345**
HRP	157 (70.1)	67 (29.9)	11.09%	**224**
N/A (under investigation or investigation closed)	**125 (85)**	**22 (15)**	7.28%	**147**
Total	**1793 (88.8)**	**227 (11.2)**	**64.55%**	**2020**

$\mathcal{X}^2$ was statistically significant, p<0.001.

The greatest proportion of the heterosexual cases had been exposed abroad and were alive. A higher proportion of men than women were exposed abroad and a higher proportion of women than men were exposed through a high risk partner (p<0.001) (table 5.15).

Table 5.15 Transmission categories for heterosexual people

	Sex		Total
Heterosexual transmission group	Female	Male	
Exposed abroad	684 (60.7)	620 (69.4)	**1304 (64.6)**
Exposed UK, Partner	187 (16.6)	158 (17.7)	**345 (17.1)**
HRP	177 (15.7)	47 (5.3)	**224 (11.1)**
N/A (under investigation or investigation closed)	79 (7.0)	68 (7.6)	**147 (7.3)**
Total	**1127 (100)**	**893 (100)**	**2020 (100)**

Those infected through a high risk partner had on average the lowest age at first report (Table 5.16).

Table 5.16 Mean age at first report for Heterosexual transmission categories

Heterosexual transmission group	Mean age at first report (years)	SD for mean age at first report
Abroad	34.9	**9.3**
UK: Partner	34.6	**10.8**
High Risk Partner (HRP)	29.7	**8.3**
N/A	33.0	**9.3**
Overall	**34.2**	**9.6**

Over half of the total heterosexual group, 52% (1050/2020), was exposed in abroad. A UK group was exposed through partner contact with someone either inside or

outside Europe, with the majority in the latter group. Others had been exposed through high risk partner (HRP) contact with the other three main transmission groups – tissue, blood and blood products transfer, IDU and MSM. There was a clear ranking between these groups in the proportion deceased, with the high risk partner group having the greatest proportion deceased.

Changes by HAART era for transmission group

In the same way as for ethnicity, chi square for trend for HAART era of first report was calculated for each category against the other categories combined. Missing and unknown transmission routes were excluded.

Table 5.17 Transmission group by HAART era of first report

Transmission group	Pre-HAART n(%)	Early HAART n(%)	Late HAART n(%)	Ultra active ART n(%)	Total N (%)	P for χ^2 for trend
Blood/Tissue Transfer	29 (1)	*	11 (1)	*	**50 (1)**	**<0.020**
Haemophiliac people	84 (3)	*	*	*	**87 (2)**	**<0.000**
Heterosexual people	458 (17)	197 (39)	435 (50)	930 (51)	**2020 (34)**	**<0.000**
IDU	1127 (42)	68 (14)	61 (7)	75 (4)	**1331 (23)**	**<0.000**
IDU+MSM	35 (1)	*	*	*	**51 (1)**	**<0.000**
MSM	893 (33)	203 (41)	322 (37)	718 (39)	**2136 (36)**	**<0.000**
Other	*	*	*	*	**14 (0)**	**Too few**
Mother to child (vertical)	28 (1)	*	16 (2)	23 (1)	**76 (1)**	**<0.375**
Total N (%)	**2678 (100)**	**501 (100)**	**868 (100)**	**1826 (100)**	**5873 (100)**	

Table 5.17 shows haemophiliac people, IDU, and 'IDU+MSM' were a decreasing proportion of patients, heterosexual people were an increasing proportion and others remained broadly the same. Heterosexual transmission subgroups were tested individually for trend in the same way, excepting the investigation closed/under investigation subgroup, with results as shown in Table 5.18:

Table 5.18 Trends for Heterosexual transmission subgroups by era first report

	Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra active ART (%)	Total (%)	P for χ^2 for trend
Exposed abroad	177 (38.5)	112 (56.9)	311(71.5)	705(75.8)	**1304(64.5)**	**<0.000**
Exposed UK, Partner	84(18.3)	44(22.3)	79(18.2)	138(14.8)	**345(17.1)**	**<0.036**
HRP	154(33.5)	30(15.2)	26(6.0)	14(1.5)	**224(11.1)**	**<0.000**
Total (100%)	**458**	**197**	**435**	**930**	**2020**	

Table 5.18 shows trends were to a decreasing proportion of high risk partners and an increasing proportion of patients who had been exposed abroad.

5.5 Earliest CD4 count (a brief note)

Table 5.19 below shows a higher percentage of deceased first reporting pre-HAART were in the earliest CD4 category 50-199, not <50. There was a statistically significant linear trend in earliest CD4 group by era of first report overall and for the deceased (p<0.007), but not for the live patients (p<0.191). The proportion in the lowest earliest CD4 group (<50) increased by era of first report in the deceased. Chi square data requirements were met overall and for the patients alive at 25.9.09, but not for the deceased. Only the overall figures are given below:

Table 5.19 Earliest CD4 count group by HAART Era of HPS first report*

Deceased or not	**HAART Era of HPS first report**					**Total**	**X^2 for trend**
	Earliest CD4 group	Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra active ART (%)		
Overall	<50	336 (17)	66 (14.4)	118 (14.8)	155 (9.8)	**675 (14)**	**<0.001**
	50-199	484 (24.5)	99 (21.6)	179 (22.5)	285 (18)	**1047 (21.8)**	
	200-349	455 (23.1)	97 (21.1)	171 (21.5)	364 (23)	**1087 (22.6)**	
	350-500	322 (16.3)	82 (17.9)	130 (16.4)	335 (21.1)	**869 (18.1)**	
	501-999	331 (16.8)	97 (21.1)	184 (23.1)	401 (25.3)	**1013 (21.1)**	
	1000+	44 (2.2)	18 (3.9)	13 (1.6)	46 (2.9)	**121 (2.5)**	
	Total overall	**1972 (100)**	**459 (100)**	**795 (100)**	**1586 (100)**	**4812 (100)**	

*cases with missing earliest CD4 count are excluded.

6. Mortality

Excluding 2009 figures for deaths and new cases, because it was not a complete year, the crude death rate per 1000 for 1981 to 2008 was 274.5.The graphic (Fig 6.1) and table 6.1 shows the decline in annual mortality rate from the introduction of HAART in 1996-7 and table 6.1 shows fuller figures for deaths.

Fig 6.1 Annual mortality rate among people recorded on the HPS HIV database, starting in 1982

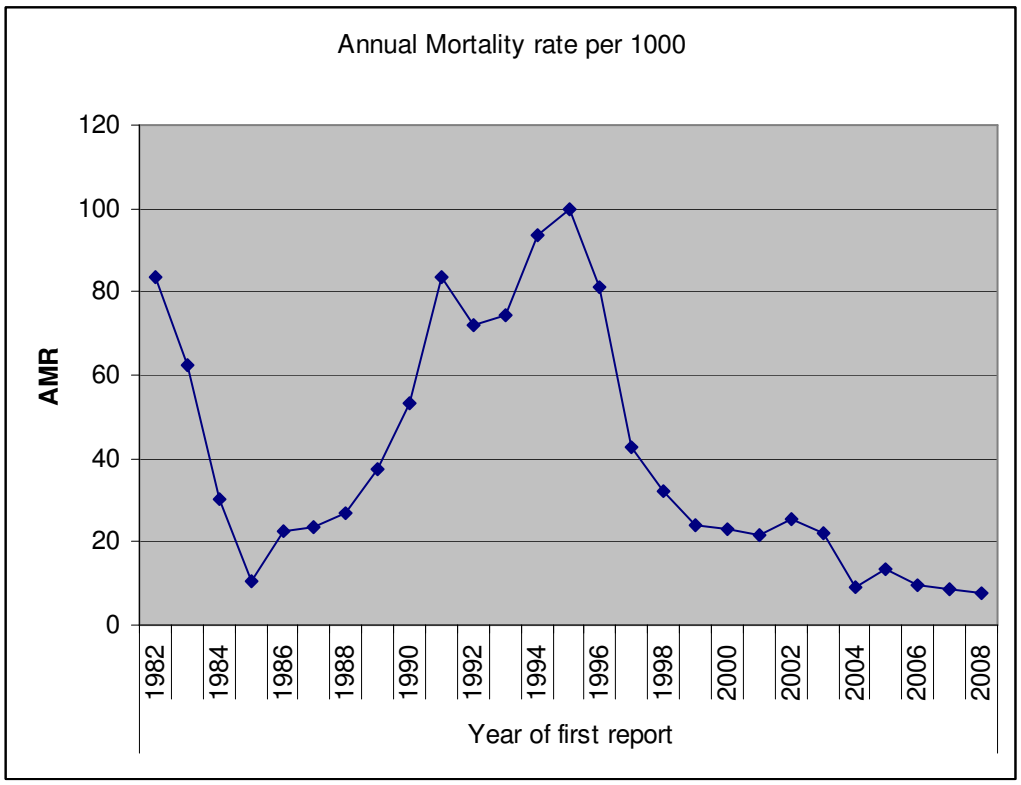


Table 6.1 Annual mortality rates by year of first report

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Entered that year	3	16	79	261	280	306	245	151	127	134	194	156	208	179	162	177	171	169	161	163	184	231	290	365	377	308	376	**320**
Entered by mid year	1	9	14	169	132	172	163	89	80	68	95	86	109	111	84	98	90	98	81	81	104	114	146	174	213	160	167	**168**
Died that year	0	1	2	8	5	18	25	33	50	74	124	111	120	159	170	138	74	59	46	47	47	59	56	25	43	33	32	**31**
Died by mid year	0	0	0	2	1	8	9	16	28	26	56	52	59	75	89	70	44	33	20	23	30	32	27	18	29	16	24	**18**
Entered to date to mid year	1	12	33	267	491	811	1108	1279	1421	1536	1697	1882	2061	2271	2423	2599	2768	2947	3099	3260	3446	3640	3903	4221	4625	4949	5264	**5641**
Died to date to mid year	0	0	1	5	12	24	43	75	120	168	272	392	510	646	819	970	1082	1145	1191	1240	1294	1343	1397	1444	1480	1510	1551	**1577**
Alive mid year	1	12	32	262	479	787	1065	1204	1301	1368	1425	1490	1551	1625	1604	1629	1686	1802	1908	2020	2152	2297	2506	2777	3145	3439	3713	**4064**
Annual Mortality rate/1000 *	**0**	**83.3**	**62.5**	**30.3**	**10.4**	**22.6**	**23.3**	**27**	**37.6**	**53.1**	**83.73**	**72**	**74.5**	**93.5**	**100**	**81.2**	**42.8**	**32.2**	**23.9**	**23**	**21.5**	**25.3**	**22.1**	**8.94**	**13.5**	**9.55**	**8.56**	**7.59**

*#deaths in one year/total midyear population

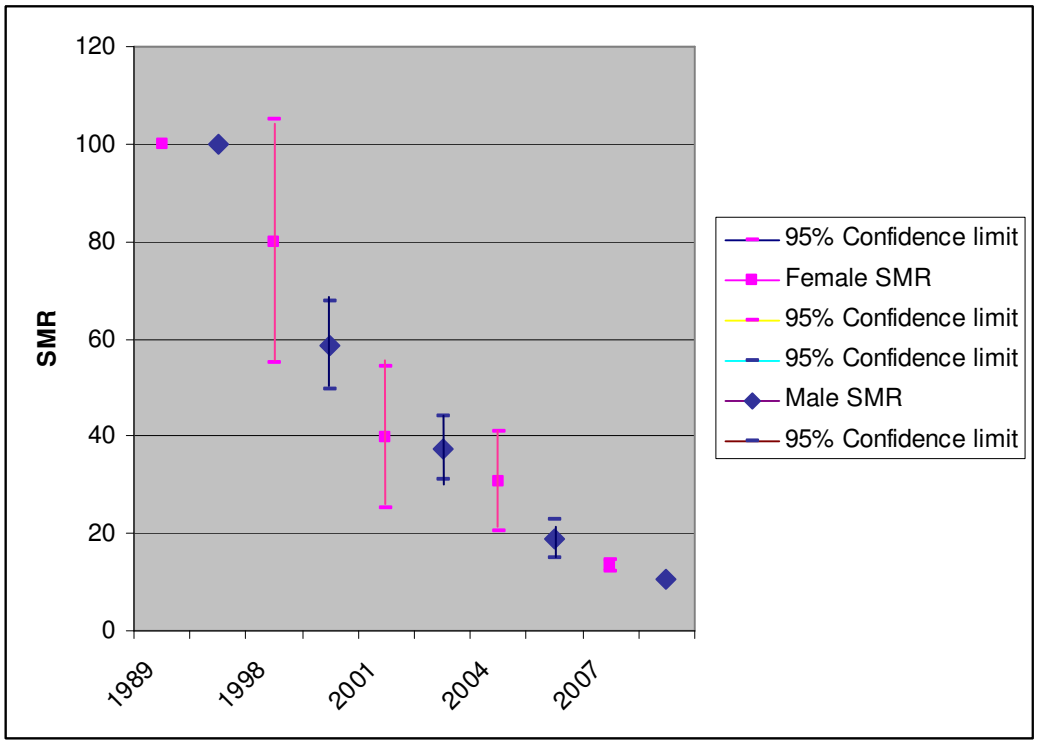
Average annual mortality rate/1000 pre-HAART 1981-1996	53.48
Average annual mortality rate/1000 Early HAART 1997-1999	32.93
Average annual mortality rate/1000 HAART 2000-2003	23.00
Average annual mortality rate/1000 Ultra active ART 2003-08	**9.64**

CMR 1981-2008 (per 1000 persons)	274.47 (1590/5793 *1000)
CMR 1981- 25/9/09 (per 1000 person-years)	31.65 (1593/50333.83 *1000)

6.1 Standardised mortality ratios

Figure 6.2 shows the downward trend for male and female standardised mortality ratios over four reference years in the three later periods. This analysis is grouped by age at death or at the reference dates as described in methods, and not by age at first report. All patients referred since the start of the database by each 30 June in the year specified, and still alive then, were the prevalent population, the deaths were actual deaths in the three years around 30 June in each year used. See appendix 8 for the data on which these figures are based, and appendix 10 for an example of SPSS syntax used.

Fig 6.2 Female and male SMR (1989 HPS HIV patients rates = SMR 100)*

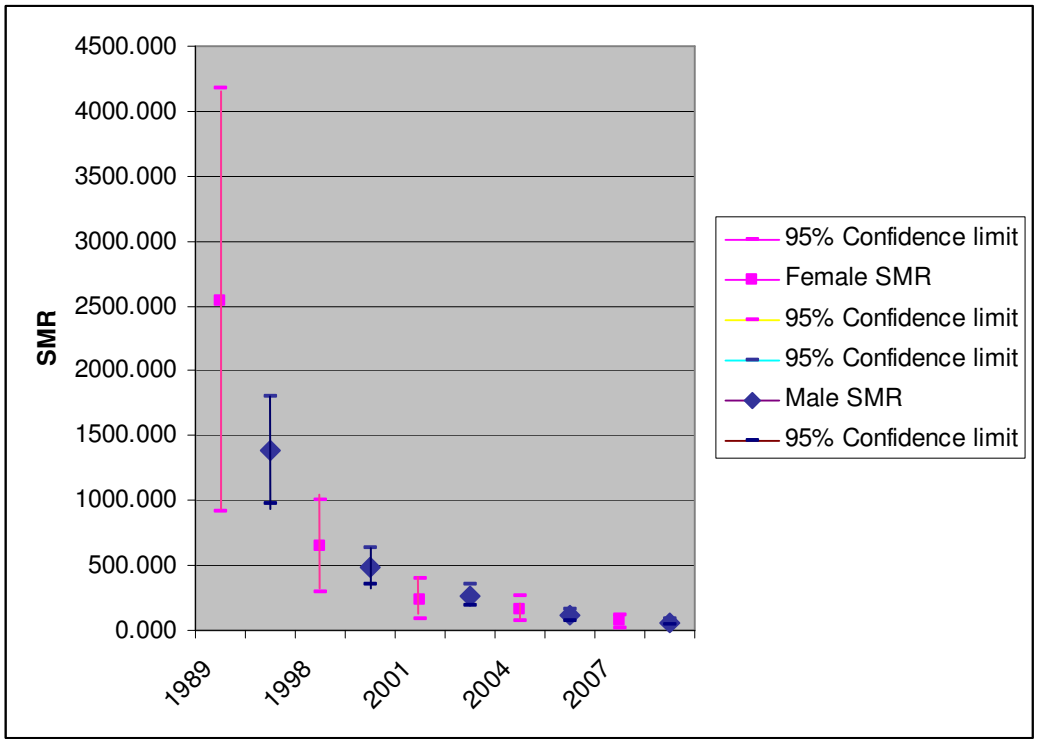


*Note the x-axis scale exaggerates the slope between 1989-98. CI for 2007 is too small to see.

Apart from the female SMR for 1998 all the 95% confidence intervals did not overlap 100.

There was also a decreasing SMR when standardised to the 2001 Scottish population (= 100) (Fig 6.3)

Fig 6.3 SMR trends for 1989-2007 with the Scottish general population as the reference population (2001 General population rates = SMR 100)*



*Note the x-axis scale exaggerates the slope between 1989-98. CI for 2007 is too small to see

The standardisation to the general population in 2001 used a similar method to the above, but the observed HPS HIV deaths over the three year period were divided by three to give a three year average for better comparison with the annual mortality in the Scottish population. The expected deaths number rose owing to the shift to an older age distribution in the HPS HIV population.

The decrease in SMR flattened out in the tail of the curve (2001-2007), in contrast to the SMR trend with reference to the 1989 HPS HIV population, (fig 6.2) which kept falling steeply.

An overall analysis using the person years in the study to derive a crude mortality rate per thousand person years was carried out for each sex. Person years were 36153.2 for males and 14180.7 for females. The 1273 male and 320 female deaths were divided by the person years for each and multiplied by one thousand to give deaths per thousand person years. There were 22.566 female deaths per thousand female person years and 35.211 male deaths per thousand male person years in the study. The overall figure for both sexes is shown in figure 6.3 above.

7. Adjusted and unadjusted risk of death over eras of HAART

7.1 Odds ratios for death controlling for era, ethnicity, sex, age and transmission route

Table 7.1 Unadjusted OR by HAART era of first report

Era	Odds Ratio	95% UCL	95% LCL	p
Pre HAART (referent)	1	-	-	**-**
Early HAART	.147	.113	.191	**<.001**
Late HAART	.064	.048	.084	**<.001**
Ultra HAART	**.024**	**.017**	**.032**	**<.001**

Table 7.1 shows the unadjusted odds ratios (OR) by era.[d] The unadjusted OR for age (years) was 0.983 (0.977-0.988, p<0.001, HL test p<0.001), and the unadjusted OR for earliest CD4 count (single units) was 0.998 (0.997-0.998, p<0.001, HL test p <0.001). Unadjusted OR for transmission group in relation to BTT is given in appendix 12, and the unadjusted ORs for sex (male referred to female) and ethnicity (white referred to all other) are as calculated in cross tabulations in section 8.3.

Binomial logistic regression was used to adjust for time (from first report of HIV to death or censoring at 25.9.09), time squared[e], and for categories of sex, age group at first report, ethnicity, transmission route, and earliest CD4 count group. The outcome was whether or not deceased by September 2009.

When stratified by HAART era of first report, earliest CD4 group was associated with death in each era (p<0.001). There was increasing likelihood of being dead for each era of first report the lower the earliest CD4 count group. Earliest CD4 count was not normally distributed in any era, medians increased from 252 in pre-HAART to 346 in ultra-active HAART. There was a highly significant, but weak, correlation between year of first report and earliest CD4 count (Kendall's tau-b, =0.097, p<0.001, Spearman's rho, =0.143, p<0.001). Earliest CD4 group was therefore included in the model as it is related to disease progression at first report.

[d] Note the unadjusted ORs agree with those that were calculated for each post HAART era compared to pre-HAART using simple crosstabulations at the end of the survival section.
[e] from first report of HIV to death or censoring at 25.9.09.

If no interaction with time was included this model (model 1a) passed the HL test ($p<0.152$). It was necessary to adjust for time (time from first report to death or censored) because survival time from first report was not normally distributed. It was more like a Poisson distribution, (numbers reduced with increased survival time). Overall mortality increased with time, and both survival and morality were each differently distributed within each era. Adding time to the model captured the increase rate, and adding time squared captured the non-linearity of the time distribution.

All the categorical variables were tested for interaction with time and time squared (model 1b). Using the probabilities (p) at the overall level for each variable, three variables interacted with time or time squared at a statistically significant degree at the 5% level. These were transmission group (with time and time squared), and age group (with time squared only) and earliest CD4 group (with time only). Only the statistically significant interactions were retained in a further model (1c), but large Odds ratios and wide confidence intervals for some of the variables meant this model needed adjustment. (HL for models 1b and 1c was $p<0.001$)

A second model (model 2a) was tried, where age and earliest CD4 count were made continuous variables in order to avoid possible small numbers in categories. All interactions were tested again as before, except the new continuous variables for age and CD4 group were used in place of the discarded ones. Transmission group and age now had significant interactions with both time and time squared at the $p<0.01$ level. Earliest CD4 interacted statistically significantly with time but not time squared ($p<0.045$). These interactions were retained in a second model (model 2b), to adjust for them. In model 2b the interaction with earliest CD4 count became statistically insignificant, so was removed to create a final model 2c with results as shown in table 7.2 below. HL statistical significance for models 2a, 2b and 2c was $p<0.001$. (scientific notation is used for very large or small numbers):

Table 7.2 Model 2c: Overall Odds ratios for death adjusted for HAART era of first report and other factors (scientific notation is used for very large or small numbers)

Variable	Adjusted OR for death	95% C.I.for Odds ratio		Sig.
		Lower	Upper	
HAART era of HPS first report (referred to pre-HAART)				**1.276E-63**
Early HAART	.009	.004	.018	**3.882E-39**

Variable	Adjusted OR for death	95% C.I.for Odds ratio		Sig.
		Lower	Upper	
Late HAART	1.844E-05	4.685E-06	7.255E-05	**7.706E-55**
Ultra active ART	6.513E-09	5.299E-10	8.005E-08	**4.416E-49**
Males (referred to females)	1.023	.675	1.548	**.916**
White (referred to non-white)	5.653	2.691	11.874	**4.773E-06**
Transmission Route (referred to Blood/tissue transfer)				**.023**
Haemophilia	9.799E-10	2.505E-16	.004	**.007**
Heterosexual	.012	1.877E-04	.826	**.040**
IDU	3.863E-04	2.772E-06	.054	**.002**
IDU+MSM	.133	5.837E-05	303.527	**.609**
MSM	.005	7.517E-05	.333	**.013**
Other	4.841E-04	2.508E-34	9.344E+26	**.830**
Mother to child (Vertical)	0.000E+00	0.000E+00	.	**.975**
Unknown	.003	2.203E-05	.381	**.019**
Age at first report (years)	1.071	1.025	1.120	**.002**
Earliest CD4 count	.999	.998	1.000	**.003**
Time from HIV first report to death or censored (years)	.132	.056	.308	**3.004E-06**
Time from HIV first report to death or censored (years) Squared	1.044	1.013	1.076	**.005**
Age at first report (years) by Time from HIV first report to death or censored (years) Squared	1.001	1.000	1.001	**.002**
Age at first report (years) by Time from HIV first report to death or censored (years)	.980	.971	.989	**3.003E-05**
Time from HIV first report to death or censored (years) * Transmission category				**.001**
Time from HIV first report to death or censored (years) by Haemophilia	.841	.739	.956	**.008**
Time from HIV first report to death or censored (years) by Heterosexual	.995	.965	1.025	**.723**
Time from HIV first report to death or censored (years) by IDU	.965	.936	.994	**.020**
Time from HIV first report to death or censored (years) by IDU+ MSM	.993	.954	1.033	**.723**
Time from HIV first report to death or censored (years) by MSM	.979	.948	1.011	**.191**
Time from HIV first report to death or censored (years) by Other	.812	.065	10.160	**.871**
Time from HIV first report to death or censored (years) by Mother to child (Vertical)	1.728E-06	0.000E+00	.	**.975**
Time from HIV first report to death or censored (years) by Unknown	1.001	.848	1.180	**.995**
Time from HIV first report to death or censored (years) Squared * Transmission category				**.001**

Variable	Adjusted OR for death	95% C.I.for Odds ratio		Sig.
		Lower	Upper	
Time from HIV first report to death or censored (years) Squared by Haemophilia	54.552	3.521	845.305	**.004**
Time from HIV first report to death or censored (years) Squared by Heterosexual	1.311	.608	2.829	**.490**
Time from HIV first report to death or censored (years) Squared by IDU	3.211	1.418	7.270	**.005**
Time from HIV first report to death or censored (years) Squared by IDU+MSM	1.290	.409	4.075	**.664**
Time from HIV first report to death or censored (years) Squared by MSM	1.761	.805	3.851	**.156**
Time from HIV first report to death or censored (years) Squared by Other	10.865	2.271E-12	5.198E+13	**.873**
Time from HIV first report to death or censored (years) Squared by Mother to child (Vertical)	1.343E+238	0.000E+00	.	**.975**
Time from HIV first report to death or censored (years) Squared by Unknown	1.345	.187	9.683	**.769**
Constant	6.744E+08			**4.506E-13**
HL test p for this model <0.001				

The fall in odds ratio for death by eras of HAART first report was much greater for the adjusted odds than the fall in the odds unadjusted for all these factors.

The adjusted odds of death in early HAART were less than 1% of the odds pre-HAART (OR in early HAART was 0.009). Adjusted ORs were still very small for some transmission groups and there were very wide CIs in some cases.

- White ethnicity was associated with a greater risk of death in comparison to other ethnic groups (nearly six times greater, OR 5.65). The 95% CI was wide (p<0.001, 95% CI 2.69-11.87).
- Males were not at statistically significantly greater risk of death than females.
- As the OR for age as a continuous variable was 1.071, with each increasing year of age at first report the odds of death increased by 7.1% in comparison to the previous year, (p<0.002, 95% CI 125-112)
- Earliest CD4 count was associated with a reduced risk of death of 0.1% for each extra unit, (OR 0.999) in comparison to the next lower CD4 count. (p<0.003, 95% CI .998-1.00)
- Compared to those contracting HIV through the blood/tissue transfer route:
  - People with haemophilia had a very small risk (p<0.007)
  - Heterosexual people had 12% of the risk (so decreased by 88%) (p<0.040)
  - IDU had a very small risk (p<0.002)

- MSM had 0.5% of the risk (so decreased by 99.5%) ($p<0.013$)
- The IDU+MSM, MTC (vertical), and 'other' transmission groups did not have statistically significantly lower odds for death than those contracting HIV through the blood/tissue transfer route.

- Time since first report was statistically significant with 13.2% (OR 0.132) of the risk of death for each additional year of time since first report in comparison to the previous year ($p<0.001$, 95% CI .056-.306).

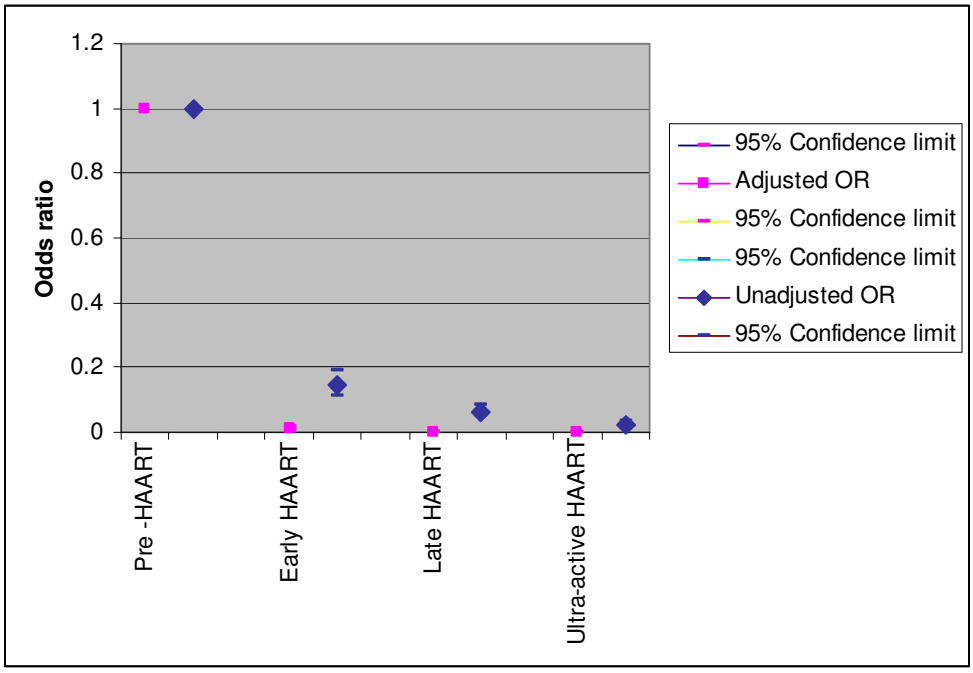
- There were significant interactions between time from first report to death or censored and age, and between time from first report to death or censored and transmission group. These were adjusted for by retaining them in the model.

Both model 1c and model 2c failed the HL test ($p<0.001$). Reasons for that could fall into two main categories:

1. not enough data, so too few cases in the live and deceased categories, this could be solved by waiting for more deaths to occur, or by more strenuous follow up of those not attending in the last five years, and
2. not enough different variables in the model. Further possible variables are suggested in the discussion.

The study was restricted on both of these factors by the data that was available. Fig 7.1 shows the drop in adjusted and unadjusted ORs over the eras in comparison to Pre-HAART. Confidence intervals are shown (except for pre-HAART as it was the referent category). CI's are very narrow, so do not show up, especially for adjusted ORs and for the ultra-active HAART period of first report.

Fig 7.1 Adjusted and unadjusted OR for death: trends compared by era



7.2 Factors associated with death within each era of first report

Model 2c was stratified by HAART era of patient first report. All the interactions tested for the overall models were tested afresh for each era.

Results of interaction tests:

- Era 1: significant interactions against time and time squared were Age and transmission group
- Era 2: SPSS reported 'error encountered in estimation' – no Odds ratios were generated
- Era 3: No significant interactions
- Era 4: One significant interaction against both time and time squared – for earliest CD4 count.

Results for final models for each era

Therefore the models were run for eras 1, 3 and 4 with only the significant interactions applicable to each era (in addition to the other variables). For era 2 the model with interactions included as for era 1 was run without problems, and that was the result used.

Table 7.3 Model 2c(i) – Pre-HAART: Odds ratios for death adjusted for other factors for Patients first reporting in HAART era One (scientific notation is used for very large or small numbers)

Variables and their values	Adjusted OR for death	Lower 95%CI	Upper 95% CI	Sig (p)
Males (referred to females)	.952	.587	1.546	**.843**
White (referred to non-white)	8.080	2.506	26.046	**4.680E-04**
Transmission Route (referred to Blood/tissue transfer)				**.022**
Haemophilia	2.827E+192	0.000E+00	.	**.992**
Heterosexual	1.734E-05	1.698E-20	1.771E+10	**.534**
IDU	3.806E-14	1.911E-28	7.578	**.066**
IDU+MSM	1.874E-13	4.618E-29	760.441	**.110**
MSM	1.836E-09	2.946E-24	1.144E+06	**.247**
Other	1.866E-28	0.000E+00	.	**.999**
Mother to child (Vertical)	0.000E+00	0.000E+00	.	**.993**
Unknown	1.439E-13	0.000E+00	.	**1.000**
Earliest CD4 count	.999	.998	1.000	**.023**
Time from HIV first report to death or censored (years)	.117	.003	4.879	**.259**
Time from HIV first report to death or censored (years) Squared	1.052	.952	1.163	**.317**
Age at first report (years) by Time from HIV first report to death or censored (years)	.893	.842	.946	**1.477E-04**
Age at first report (years)	2.133	1.325	3.435	**.002**
Transmission Route (referred to Blood/tissue transfer) * time from first report to death or censored				**.001**
Haemophilia * time from first report to death or censored	3.151E-20	0.000E+00	.	**.992**
Heterosexual * time from first report to death or censored	4.740	.087	257.590	**.445**
IDU * time from first report to death or censored	83.671	1.912	3660.986	**.022**
IDU+MSM * time from first report to death or censored	55.640	.858	3607.432	**.059**
MSM * time from first report to death or censored	16.395	.315	852.843	**.165**
Other * _time from first report to death or censored	1.709E+07	0.000E+00	.	**.999**
Mother to child (Vertical) * time from first report to death or censored	1.694E+295	0.000E+00	.	**.993**
Unknown * time from first report to death or censored	2221.276	0.000E+00	.	**1.000**
Time from HIV first report to death or censored (years) Squared * Transmission category				**2.949E-04**
Time from HIV first report to death or censored (years) Squared by Haemophilia	2.758	2.680E-100	2.838E+100	**.993**
Time from HIV first report to death or censored (years) Squared by Heterosexual	.950	.850	1.060	**.358**
Time from HIV first report to death or censored (years) Squared by IDU	.871	.785	.966	**.009**
Time from HIV first report to death or censored (years) Squared by IDU+MSM	.884	.787	.993	**.038**
Time from HIV first report to death or censored (years) Squared by MSM	.912	.817	1.018	**.100**
Time from HIV first report to death or censored (years) Squared by Other	.384	0.000E+00	.	**.999**
Time from HIV first report to death or censored (years) Squared by Mother	7.139E-08	0.000E+00	.	**.993**

Variables and their values	Adjusted OR for death	Lower 95%CI	Upper 95% CI	Sig (p)
to child (Vertical)				
Time from HIV first report to death or censored (years) Squared by Unknown	.604	0.000E+00	.	**1.000**
Age at first report (years) by Time from HIV first report to death or censored (years) Squared	1.004	1.002	1.005	**.000**
Constant	1.883E+08			**.265**
HL test for this model p<0.005				

In those first reporting in the pre-HAART era statistically significant odds ratios were found (table 7.3) as follows:

- White people were more than eight times more likely to die than non white people (OR 8.08) (95% CI was wide, 2.51-26.04, p<0.001).
- As the OR for age as a continuous variable was 2.133 (1.33-3.44, p<0.001), with each increasing year of age at first report the odds of death increased by 113.3% in comparison to the previous year
- Earliest CD4 count was associated with a reduced risk of death of 0.1% for each extra unit in comparison to the next lower CD4 count (OR 0.999, 0.998-1.000, p<0.023).
- Although transmission route was related to risk of death overall (p<0.022), no one transmission category had an individually statistically significantly different OR for death compared to blood tissue transfers.

There were statistically significant interactions between time from first report to death or censored and transmission category, and age (with time squared) these were retained in the model to adjust for them.

Table 7.4 Model 2c(ii) Early HAART: Odds ratios for death adjusted for other factors for Patients first reporting in HAART era two (scientific notation is used for very large or small numbers)

Variables and their values	Adjusted OR for death	Lower 95%CI	Upper 95% CI	Sig (p)
Males (referred to females)	.749	.080	6.974	**.799**
White (referred to non-white)	.138	.010	1.871	**.137**
Transmission Route (referred to Blood/tissue transfer)				**1.000**
Haemophilia	.008	0.000E+00	.	**1.000**
Heterosexual	0.000E+00	0.000E+00	.	**1.000**
IDU	0.000E+00	0.000E+00	.	**1.000**
IDU+MSM	0.000E+00	0.000E+00	.	**1.000**
MSM	0.000E+00	0.000E+00	.	**1.000**

Variables and their values	Adjusted OR for death	Lower 95%CI	Upper 95% CI	Sig (p)
Other	1.775E-46	0.000E+00	.	1.000
Mother to child (Vertical)	0.000E+00	0.000E+00	.	1.000
Unknown	0.000E+00	0.000E+00	.	1.000
Earliest CD4 count	1.001	.998	1.004	.437
Time from HIV first report to death or censored (years)	2.133E-68	0.000E+00	.	1.000
Time from HIV first report to death or censored (years) Squared	1006.342	0.000E+00	.	1.000
Age at first report (years) by Time from HIV first report to death or censored (years)	.803	.195	3.299	.761
Age at first report (years)	4.202	.002	7122.542	.705
Transmission Route (referred to Blood/tissue transfer) * time from first report to death or censored				1.000
Heterosexual * time from first report to death or censored	1.387E+95	0.000E+00	.	.999
IDU * time from first report to death or censored	2.224E+69	0.000E+00	.	1.000
IDU+MSM * time from first report to death or censored	5.761E+70	0.000E+00	.	1.000
MSM * time from first report to death or censored	6.738E+64	0.000E+00	.	1.000
Other * censored	18540.601	0.000E+00	.	1.000
Mother to child (Vertical) * time from first report to death or censored	3.009E+103	0.000E+00	.	1.000
Unknown * time from first report to death or censored	7.743E+72	0.000E+00	.	1.000
Time from HIV first report to death or censored (years) Squared * Transmission category				.999
Time from HIV first report to death or censored (years) Squared by Heterosexual	1.737E-06	0.000E+00	.	.999
Time from HIV first report to death or censored (years) Squared by IDU	8.411E-04	0.000E+00	.	1.000
Time from HIV first report to death or censored (years) Squared by IDU+MSM	5.189E-04	0.000E+00	.	1.000
Time from HIV first report to death or censored (years) Squared by MSM	1.357E-03	0.000E+00	.	1.000
Time from HIV first report to death or censored (years) Squared by Mother to child (Vertical)	3.600E-05	0.000E+00	.	1.000
Time from HIV first report to death or censored (years) Squared by Unknown	3.284E-04	0.000E+00	.	1.000
Age at first report (years) by Time from HIV first report to death or censored (years) Squared	1.008	.942	1.078	.822
Constant	.			1.000
HL test for this model p<0.792				

In those first reporting in the early HAART era (table 7.4) no statistically significant odds ratios were found for any variable or any interaction. The same model was run without any interactions when it also gave non-statistically significant results, except for time (a very small OR and p<0.038) Perhaps in this era things were changing over time so fast with the introduction of HAART that the time effect was more important than anything else.

Table 7.5 Model 2c(iii) Late HAART: Odds ratios for death adjusted for other factors for Patients first reporting in HAART era three (scientific notation is used for very large or small numbers)

Variables and their values	Adjusted OR for death	Lower 95%CI	Upper 95% CI	Sig (p)
Males (referred to females)	2782.055	1.145E-68	6.757E+74	.925
White (referred to non-white)	7782.600	5.888E-71	1.029E+78	.918
Transmission Route (referred to Blood/tissue transfer)				.335
Heterosexual	.006	3.323E-05	1.057	.052
IDU	.009	1.419E-05	5.738	.153
IDU+MSM	.353	.003	37.902	.662
MSM	.028	.001	.705	.030
Other	3.118E-04	0.000E+00	.	.999
Mother to child (Vertical)	1.364E-04	0.000E+00	.	1.000
Unknown	1.452E-05	0.000E+00	.	1.000
Earliest CD4 count	.997	.991	1.003	.367
Time from HIV first report to death or censored (years)	4.618E-06	2.269E-10	.094	.015
Time from HIV first report to death or censored (years) Squared	2.170	1.103	4.266	.025
Age at first report (years)	.990	.873	1.123	.879
Constant	1.058E+13			.734
HL test for this model =p<0.099				

In those first reporting in the late HAART era (table 7.5) there was one statistically significant difference in ORs at the p<0.05 level. This was for MSM who had 2.8% of the risk of death of the reference category (blood tissue transfers), but with wide CIs suggesting small numbers (OR 0.028, 0.001-0.705, p<0.030). Heterosexuals had 0.6% of the risk of the reference category, but the difference was not (quite) statistically significant (p<0.052). Time was statistically significant with a very small risk of death for each additional year in comparison to the previous year since first report to death or censored (p<0.015). Small numbers of deaths have resulted in low significance for some transmission categories' ORs

Table 7.6 Model 2c(iv), Ultra-active HAART: Odds ratios for death adjusted for other factors for Patients first reporting in HAART era four (scientific notation is used for very large or small numbers)

Variables and their values	Adjusted OR for death	Lower 95%CI	Upper 95% CI	Sig (p)
Males (referred to females)	1.799	.379	8.544	.460
White (referred to non-white)	3.361	.794	14.219	.100
Transmission Route (referred to Blood/tissue transfer)				.445
Heterosexual	1.371E-07	0.000E+00	.	1.000
IDU	.035	.002	.710	.029
IDU+MSM	.076	.002	2.447	.146

Variables and their values	Adjusted OR for death	Lower 95%CI	Upper 95% CI	Sig (p)
MSM	7.309E-09	0.000E+00	.	**.999**
Other	.040	.002	.836	**.038**
Mother to child (Vertical)	1.749E-08	0.000E+00	.	**.999**
Unknown	.007	1.324E-04	.369	**.014**
Earliest CD4 count	.987	.978	.995	**.003**
Time from HIV first report to death or censored (years)	.006	.001	.031	**1.236E-09**
Time from HIV first report to death or censored (years) Squared	2.113	1.570	2.844	**7.996E-07**
Age at first report (years)	1.031	.986	1.078	**.179**
Earliest CD4 count * Time from HIV first report to death or censored (years)	1.011	1.003	1.020	**.007**
Earliest CD4 count * Time from HIV first report to death or censored (years) squared	.998	.996	1.000	**.020**
Constant	39.598			**.082**
HL test for this model =p<0.009				

In those first reporting in the ultra-active HAART era, (table 7.6) although transmission route was not statistically significant overall, there was a statistically significantly lower risk of death for people with some of the individual transmission routes than for blood tissue transfers. These were:

- IDU who had 3.5% of the risk (OR 0.035, 0.002-0.710, p<0.029)
- Other who had 4% of the risk (OR 0.040, 0.002-0.836, p<0.038
- Unknown who had 0.7% of the risk (OR0.007, <0.001-0.369, p<0.014)

There was a decreased risk for each additional unit of CD4 count of 1.3% in comparison to the risk for the previous unit of CD4 count. (OR 0.987, 0.978-0.995, p<0.003). Although white people and males had high ORs in comparison to other ethnicity and females, because of the small numbers of deaths CIs were wide and the difference was not statistically significant. Small numbers of deaths have resulted in low significance for some transmission categories' ORs.

Exact logistic regression

Exact logistic regression is a statistical method developed by Mehta and Patel (1995).[154] It can be applied to binary logistic regression when small numbers occur, for example in the situation above, through stratification, making the performance of hypothesis tests using methods such as "the wald, the likelihood ratio or the efficient scores statistics" unreliable. Had there been time, these techniques could have been further investigated.

8. Survival time

Twenty nine of the 5902 cases were excluded from survival time analyses (see case flow diagram in methods). Two were recorded as dead in the input data. One of these had a wrong date problem – undetermined whether the wrong date was either first report or death, and one was recorded as not deceased in one of the source files but had cause of death data in the other, so it was unclear whether the individual was alive or dead. One had no date of first report. The other 26 had apparently unlikely birthdates and no date of death.

8.1 Overall survival time

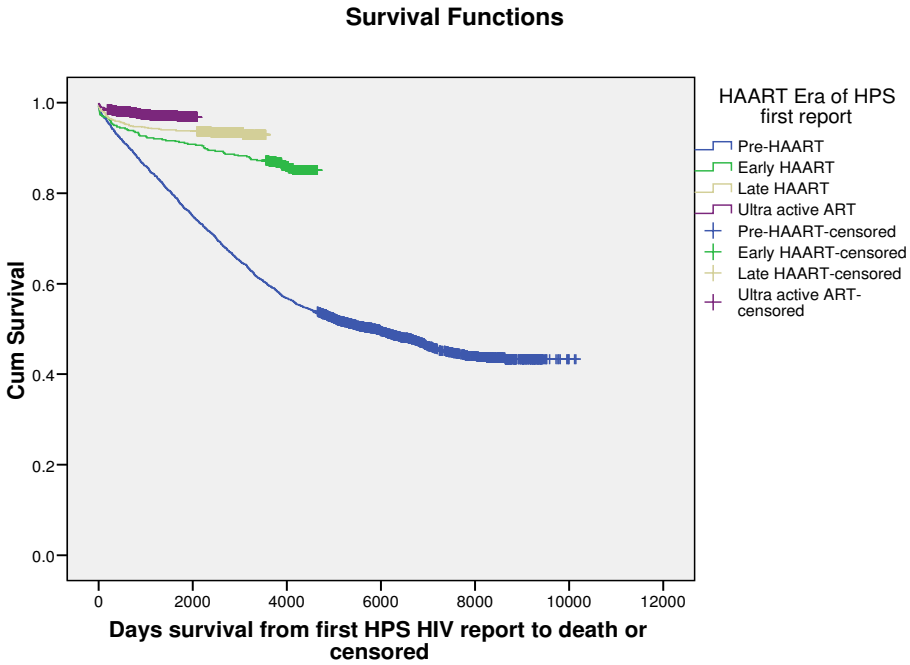
Table 8.1 Overall cases and mean days' survival from first HPS report

Case Processing Summary					Mean			
HAART Era of HPS first report	Total N	N of Events	Censored		Estimate	Std. Error	95% Confidence Interval	
			N	Percent			Lower Bound	Upper Bound
Pre-HAART	2678	1417	1261	47.1	5944	79	5790	**6099**
Early HAART	501	71	430	85.8	4182	56	4073	**4291**
Late HAART	868	58	810	93.3	3344	27	3292	**3396**
Ultra active ART	1826	47	1779	97.4	2039	7	2025	**2053**
Overall	**5873**	**1593**	**4280**	**72.9**	**6854**	**66**	**6726**	**6983**

Table 8.1 shows the mean days' survival estimates from the SPSS Kaplan Meier survival dialogue, with CIs. SPSS produced a median survival time estimate for those diagnosed pre-HAART only. It was 5889 (5298-6479) days.

Death was the event of interest. Survival curves from first HIV report to HPS to death or censored (if still alive at the date of data extraction, 25.09.2010) were plotted using the Kaplan Meier method in SPSS (Fig 8.1). Days' survival from first report to HPS was the time, 'whether dead' was the status and HAART era of first report was the factor.

Fig 8.1 Kaplan Meier overall survival time from HIV first report to HPS to death or censored* for the four HAART eras of diagnosis.

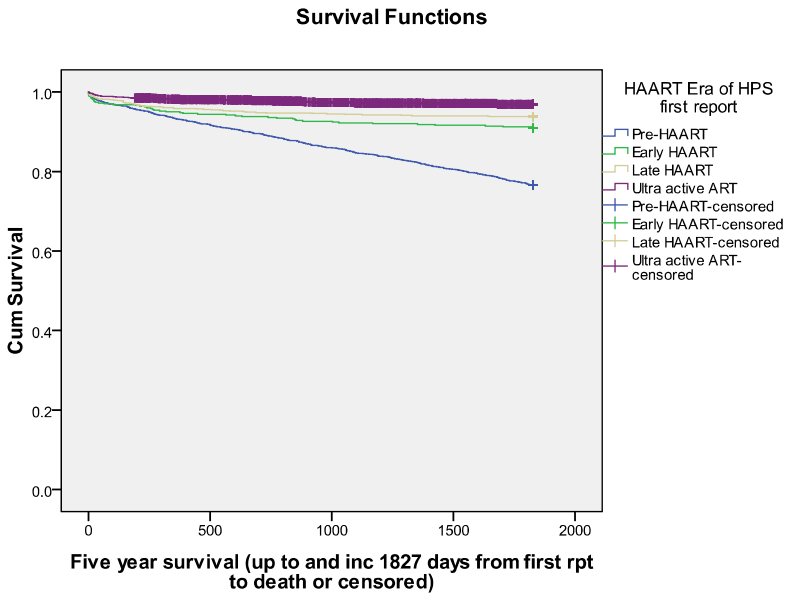


* at date of data extraction 25.9.09

A log rank test was used to compare the four survival curves (factors) and to test whether they were statistically significantly different. This gave a highly significant result ($p<0.001$) showing there was a continuing improvement over the four eras.

A five year survival plot is shown below (fig 8.2. Here death within five years of first report was the event of interest. Cases were censored if surviving over five years after first report (whether or not they had died later) and were censored if alive but had not yet had five years after first report. Thus for the three earliest HAART eras censoring occurs only at the end of the five year period (at 1828 days), but for the ultra active period, cases who had not yet had five years after first report are censored at earlier times after first report.

Fig 8.2 Five year survival from HIV first report to HPS to death or censored*



*at five years survival or earlier than five years if alive less than five years after first report at date of data extraction

Again the log rank test was highly significant ($p<0.001$)

A Cox's proportional hazards model (assuming the ratio of hazards is equal at all time points) was fitted to five year survival data to test the null hypothesis of 'equal hazards' for the three treatment groups. Results are below (table 8.2)

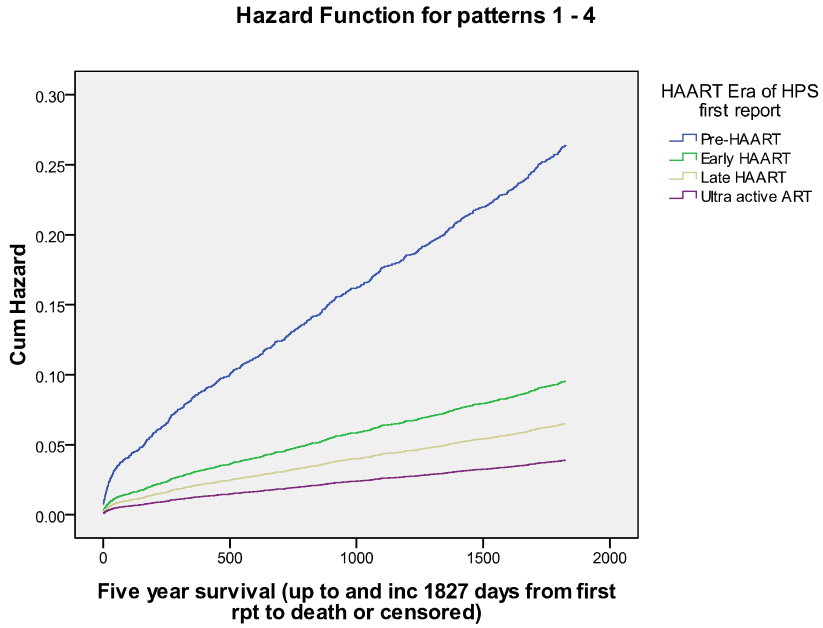
Table 8.2 Hazard ratios for death within five years of first report

Comparison	Hazard Ratio for death, from Cox Proportional hazards model	95.0% CI for Hazard ratio		Sig.
		Lower	Upper	
Difference for HAART eras overall	-	-	-	0.001
Early HAART compared to pre-HAART	.362	.267	.490	0.001
Late HAART compared to pre-HAART	.247	.187	.326	0.001
Ultra-active HAART compared to pre-HAART	.148	.110	.199	0.001

There was a 63.8% fall in early HAART, 75.3% fall in late HAART and 85.2% fall in ultra-active HAART in the hazard ratio for death within five years of first report. The pre-HAART period was the reference category. The significance is in agreement with the log rank test for Kaplan Meier, which did not require the proportional hazards assumption.

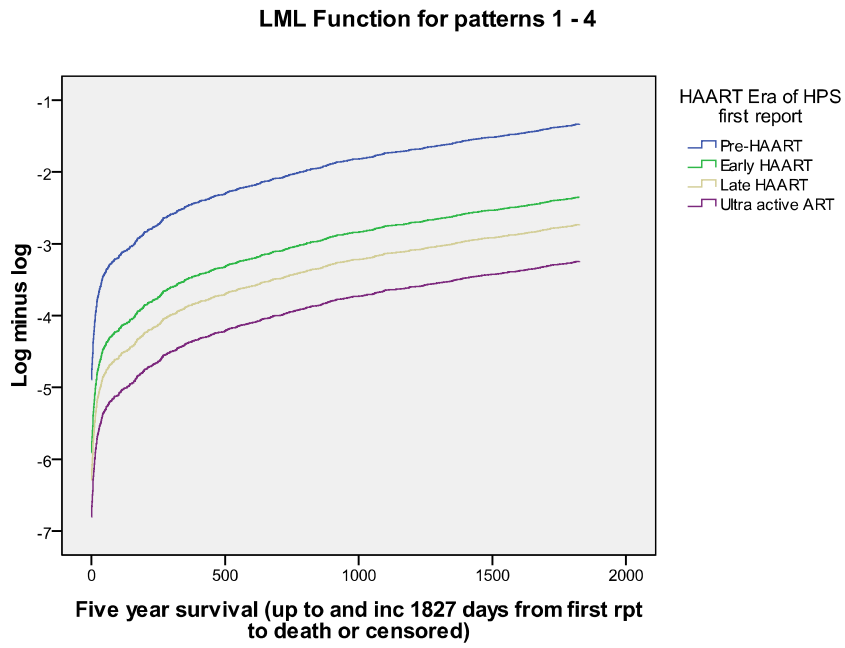
The Cox hazards curves are plotted below (fig 8.3) to give a graphic view of the risk over time:

Fig 8.3 Cox's Hazard function plot for five year survival time for four eras.



To check the proportional hazards model a log minus log plot (Fig 8.4) was run for the overall survival, which supported the proportional hazards assumption as not unreasonable, since the curves were an approximately equal distance apart over time showing the log of hazards was proportional between the eras over the time.

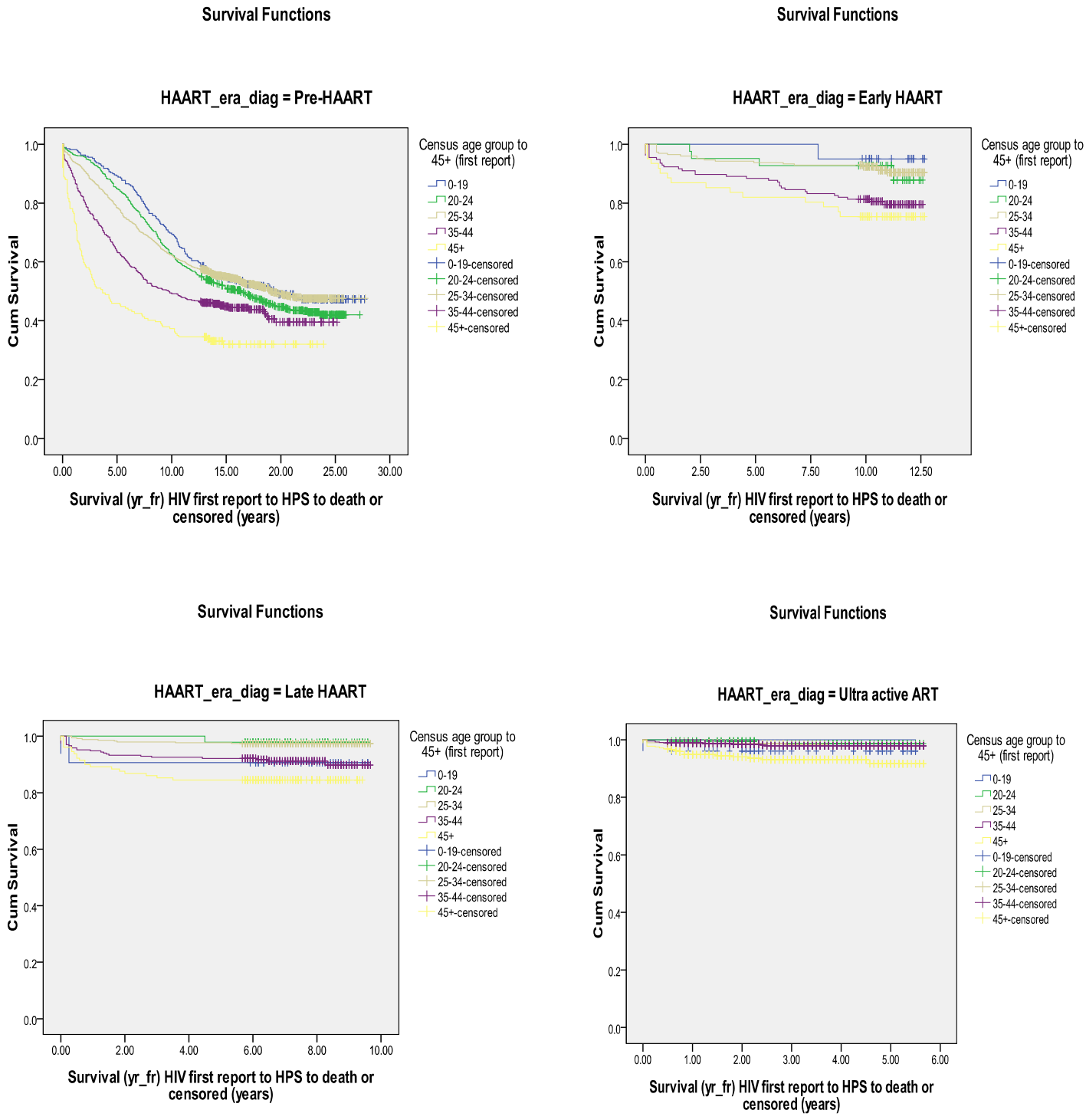
Fig 8.4 Log minus log plot for overall survival time by era



Further overall survival plots were carried out for demographic variables. The event of interest was death. Cases were censored if still alive at 25.9.09.

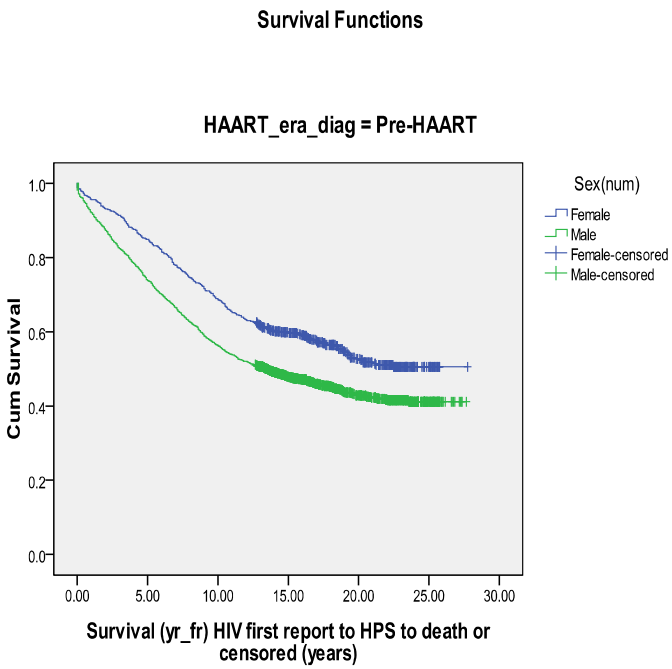
8.2 Survival times by era of HAART first report and demographic groups

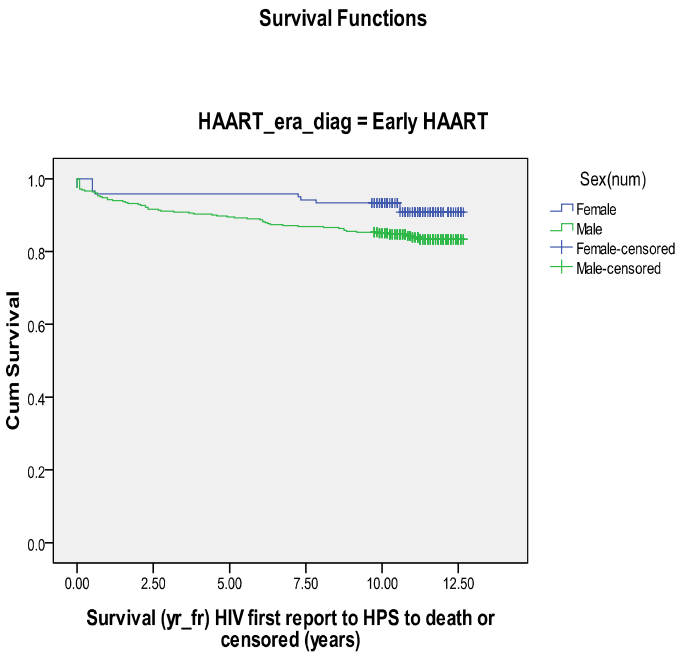
Fig 8.5 Survival time plots for age groups by era of HAART first report

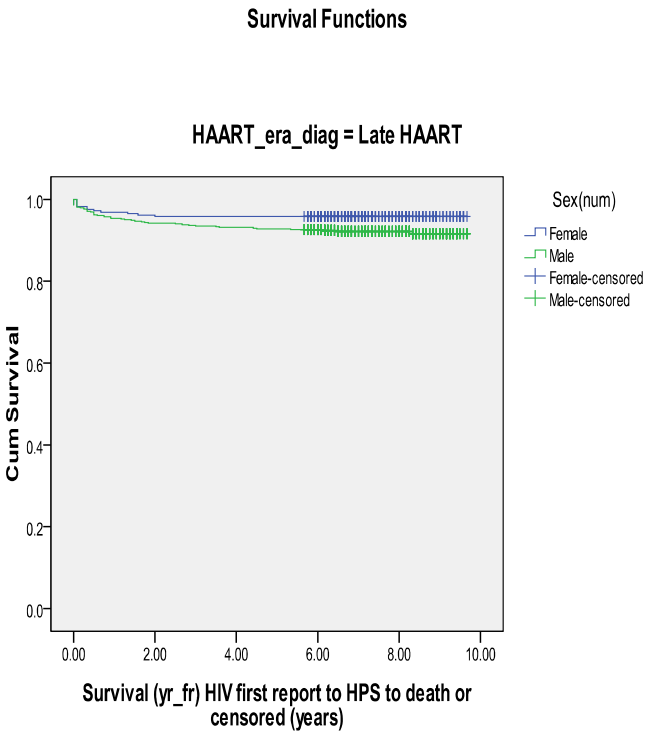


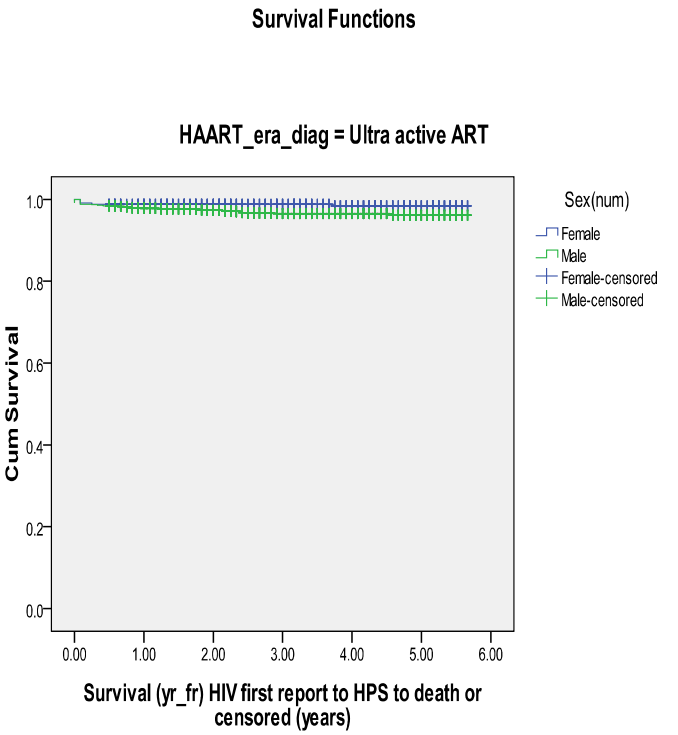
The statistical significance of differences in survival time between age groups overall, from the log rank test was $p<0.001$, showing there was a statistically significant difference in survival time between the groups over all the HAART eras. The SPSS file was split to get separate log rank tests within each era. For pre-HAART, $p<0.001$, early HAART, $p<0.002$, late HAART, $p<0.001$, ultra-active HAART $p<0.001$. Thus there was evidence of a real difference in survival time between age groups in all eras.

Fig 8.6 Survival time plots for sex groups by era of HAART first report



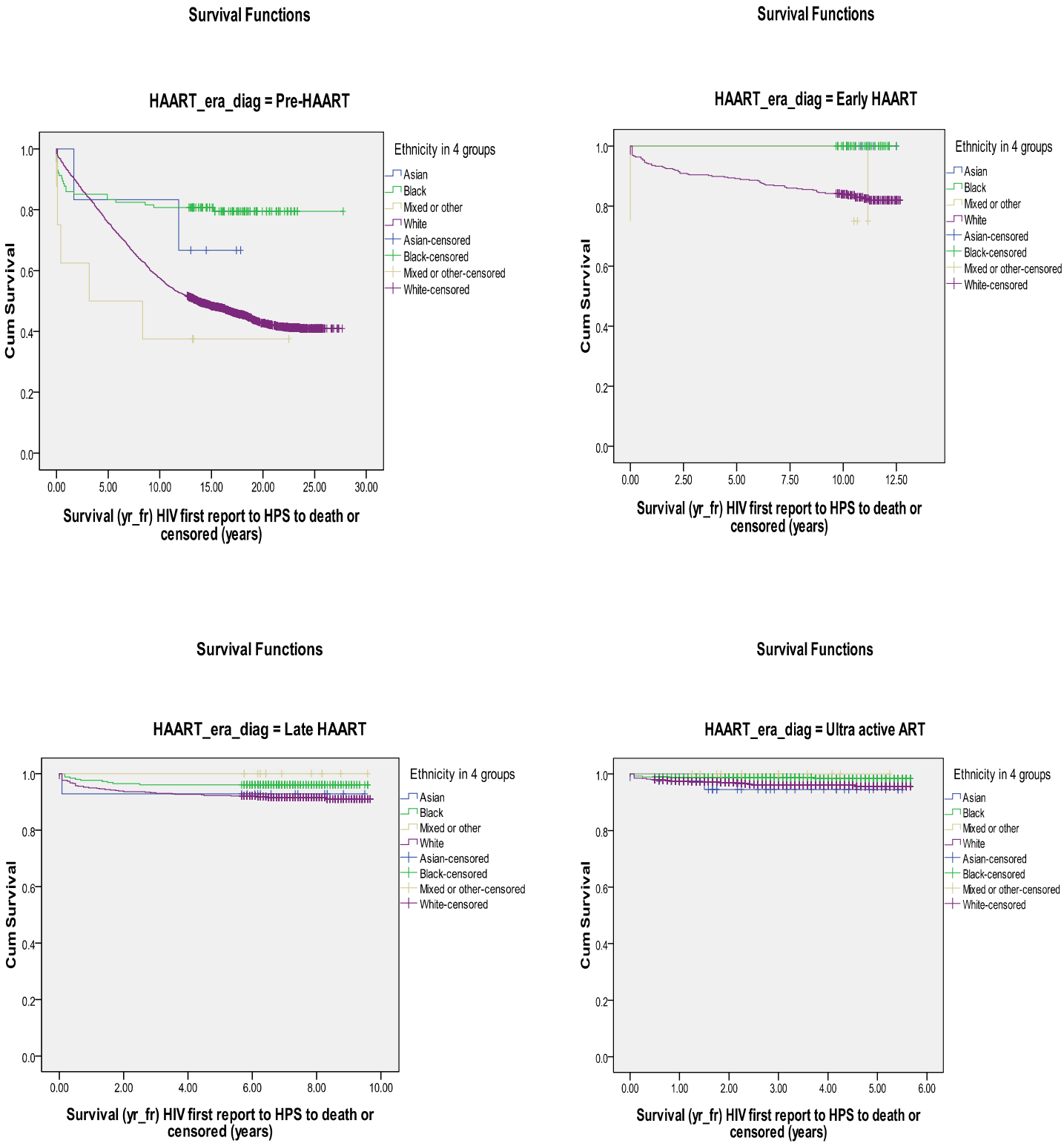






The statistical significance of differences in survival time between sexes overall, from the log rank test was $p<0.001$, showing there was a statistically significant difference in survival time between the groups over all the HAART eras. The SPSS file was split to get separate log rank tests within each era. For pre-HAART, $p<0.001$, early HAART, $p<0.039$, late HAART, $p<0.045$, ultra-active HAART $p<0.027$. Thus there was evidence of a real difference in survival time between sexes in all eras.

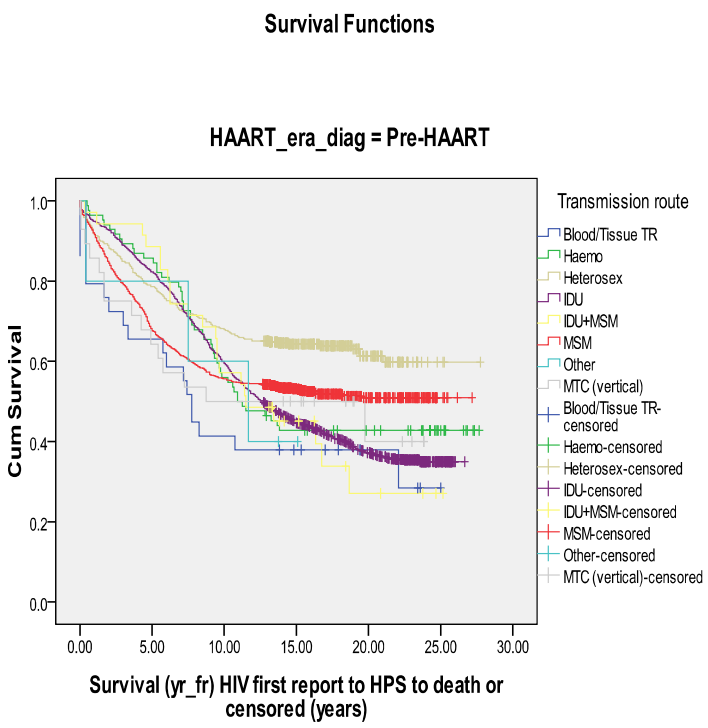
Fig 8.7 Survival time plots for ethnic groups by era of HAART first report

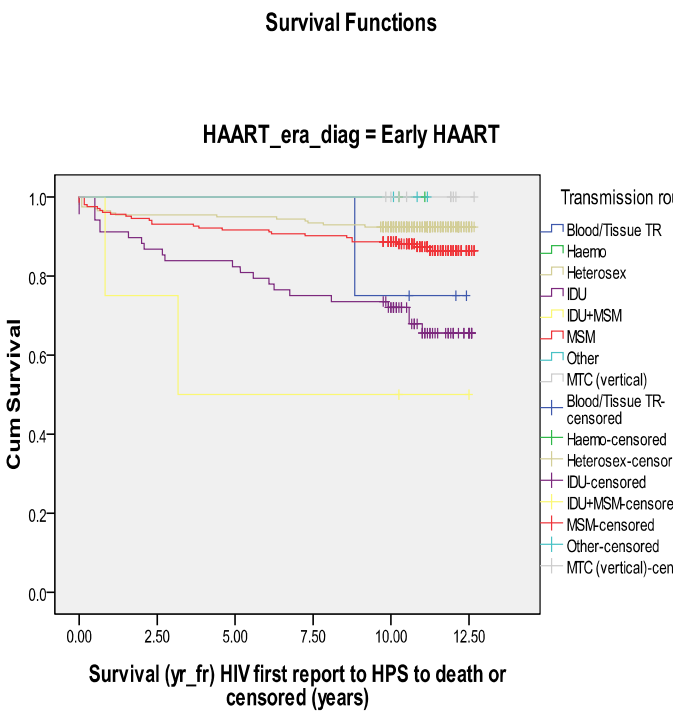


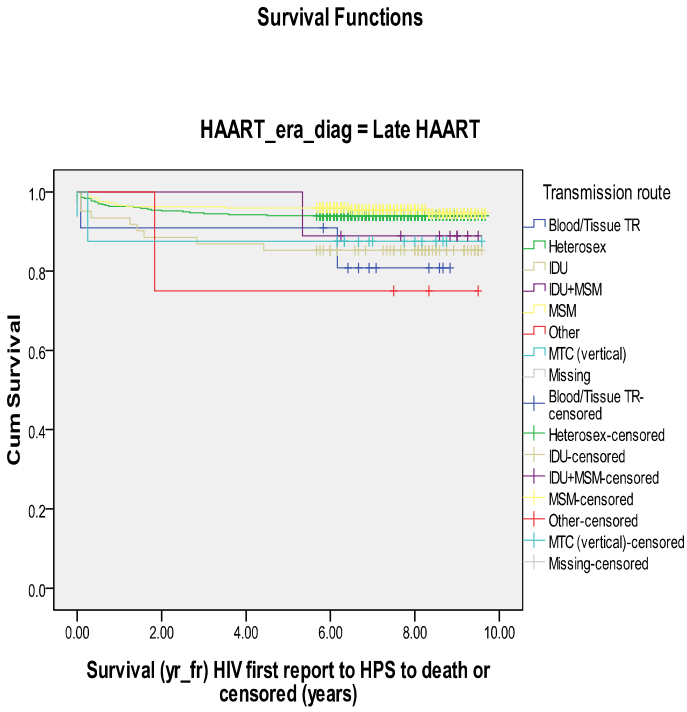
The statistical significance of differences in survival time between ethnic groups overall, from the log rank test was $p<0.001$, showing there was a statistically

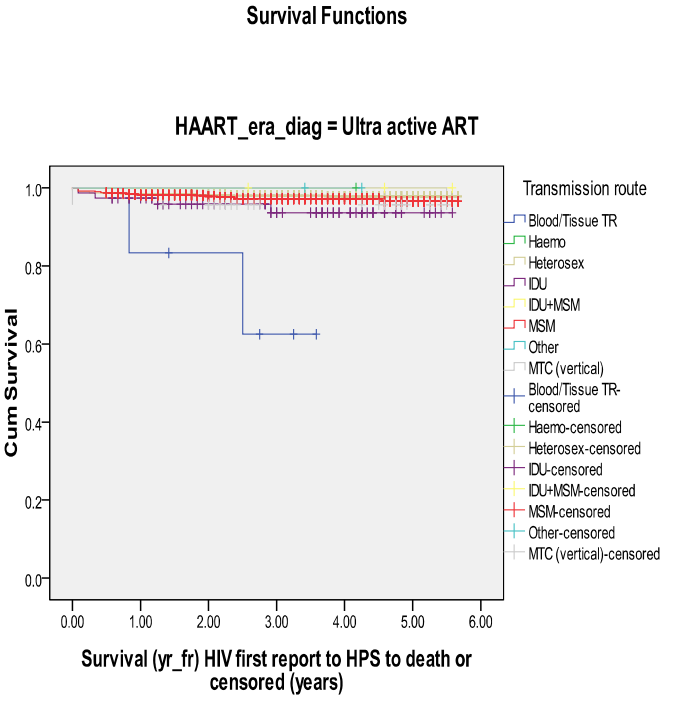
significant difference in survival time between the groups over all the HAART eras. The SPSS file was split to get separate log rank tests within each era. For pre-HAART, $p<0.001$, early HAART, $p<0.003$, late HAART, $p<0.103$, ultra-active HAART $p<0.051$. Thus there was evidence of a real difference in survival time between ethnic groups in the pre and early HAART eras only. For those first reporting in early HAART, the survival curve for 'mixed other' is affected by small total numbers of those deceased and those live at 25.9.09. No Asian and black people first reporting in early HAART died, so their survival lines overlap.

Fig 8.8 Survival time plots for transmission groups by era of HAART first report









The statistical significance of differences in survival time between those with different transmission routes overall, from the log rank test was p<0.001, showing there was a statistically significant difference in survival time between the groups over all the HAART eras. The SPSS file was split to get separate log rank tests within each era. For pre-HAART, p<0.001, early HAART, p<0.001, late HAART, p<0.022, ultra-active HAART p<0.001. Thus there was evidence of a real difference in survival time between transmission groups in all eras.

8.3 Individual risk and demographic factors

Odds ratios for death

Using simple cross tabulations and ORs from SPSS (ORs confirmed by manual calculation), this section provides unadjusted odds ratios, for the main demographic variables, compared to all other values for the variable, for death overall. This SPSS function does not provide significance tests for the OR, but it does give 95% confidence limits. Where the 95% confidence limits for the OR do not include 1, there is at least a 95% statistical probability the OR for the value concerned is different from the other values. This is like a statistical significance (p) of <0.05. Where expected counts were large enough (see methods), the χ^2 significance, which SPSS does produce, is given in the tables below if applicable. The unadjusted ORs provide a lead in to the use of logistic regression in the analysis of this subject, which adjusts the factors in relation to HAART era of first report and each other in more complex models.

Age

Table 8.3 unadjusted Odds for death for each age group

Age group	Deceased (n=1593)	Alive (n=4280)	Total (n=5873)	OR for death	Lower 95% CL	Upper 95% CL	P for χ^2
0-19	143	228	371	1.8	1.4	2.2	**<0.001**
other	1450	4052	5502				
20-24	374	603	977	1.9	1.6	2.2	**<0.001**
Other	1219	3677	4896				
25-34	585	1788	2373	0.8	0.7	0.9	**<0.001**
Other	1008	2492	3500				
35-44	318	1154	1472	0.7	0.6	0.8	**<0.001**
Other	1275	3126	4401				
45+	173	507	680	0.9	0.8	1.1	**<0.294**
Other	1420	3773	5193				

The higher odds of death were seen in the 0-19 and 20-24 age groups (p<0.001). The confidence intervals for age groups are generally narrow. Only the 45+ interval includes one, and as expected, chi square is not statistically significant.

Sex

Males had statistically significantly greater unadjusted Odds of death than females, (Table 8.4 gives frequencies) OR 1.74 (95% CL 1.52-2.0, p for χ^2<0.001).

Table 8.4 Whether deceased (by sex)

Sex	Deceased	Alive	Total
Male	1273	2976	**4249**
Female	320	1304	**1624**
Total	**1593**	**4280**	**5873**

Ethnicity

White people had the greatest unadjusted odds of death overall, at nearly eleven times the odds in all other ethnic groups, and although the confidence interval was wide, it was well away from including one, so this was highly statistically significant (see table 8.5).

Table 8.5 ORs for whether deceased by Ethnicity

Ethnic group	Deceased (n=1593)	Alive (n=4280)	Total (n=5873)	OR for death	Lower 95% CL	Upper 95% CL	P for χ^2
White	1524	2864	4388	10.920	8.509	14.015	**<0.001**
All other	69	1416	1485				
Black	41	957	998	.092	.067	.126	**<0.001**
All other	1552	3323	4875				
Asian	*	*	70	.204	.082	.508	**n/a**
All other	1588	4215	5803				
Mixed or other	*	*	36	.536	.223	1.289	**<0.157**
All other	1587	4250	5837				

Black people had statistically significantly lower odds of being dead than other groups. The confidence interval was also narrow.

Transmission

Those with HIV transmission through intravenous drug use (table 8.6) had the greatest unadjusted odds of death, OR 5.464 (95% CL 4.791-6.231, p for χ^2<0.001). IDU had a statistically significantly increased odds of death compared to other HIV positive patients at the 5% level. The CI for IDU was also quite narrow.

Table 8.6 Death by whether IDU transmission

	Deceased	Alive	Total
IDU	742	589	**1331**
All other	851	3691	**4542**
Total	**1593**	**4280**	**5873**

Table 8.7 compares Odds for death in each of the other transmission groups with odds for death in all the other transmission groups together. IDU/MSM, haemophiliac people and blood tissue transfer transmission had statistically significantly greater odds than others. Heterosexual people and MSM had statistically significantly lower odds of death than other transmission groups. Confidence intervals for Chi square confirm this, e.g. for haemophiliac people.

Table 8.7 OR for death by risk group

Risk group	Deceased (n=1593)	Alive (n=4280)	Total (n=5873)	OR for death	Lower 95% CL	Upper 95% CL	P for χ^2
Blood/tissue	24	26	50	2.503	1.433	4.372	**<0.001**
All other	1569	4254	5823				
Haemophiliac	48	39	87	3.378	2.205	5.176	**<0.001**
All other	1545	4241	5786				
Heterosexual	227	1793	2020	0.230	0.198	0.269	**<0.001**
All other	1366	2487	3853				
IDU and MSM	25	26	51	2.609	1.502	4.531	**<0.001**
All other	1568	4254	5822				
MSM	487	1649	2136	0.703	0.621	0.795	**<0.001**
All other	1106	2631	3737				
Other	*	*	14	1.075	0.337	3.432	**n/a**
All other	1589	4270	5859				
Mother to Child (vertical)	18	58	76	0.832	0.489	1.416	**<0.497**
All other	1575	4222	5797				

Odds ratios for Death with AIDS and death with Hepatitis

For transmission group only, this section gives ORs for death with AIDS or hepatitis as any cause of death. Note 'death with AIDS' means with AIDS as any cause of death, 'death from AIDS', means with AIDS as the primary cause of death.

The risk groups had different ORs for developing AIDS (perhaps related to HAART era). Table 8.8 shows AIDS ORs for each transmission group in comparison to other HIV+ people on the database, using data for deceased patients with COD.

AIDS

Table 8.8 OR for AIDS (any COD position) by risk group

Risk group	AIDS (n=906)	Not AIDS (n=285)	Total n=1191	OR for having AIDS	95% CL lower	95% CL upper	P for χ^2
Blood/tissue	13	*	*	0.815	0.288	2.307	**<0.7**
All other	894	281	1175				
Haemophilia	19	16	35	0.360	0.183	0.710	**<0.002**
All other	888	270	1158				
Heterosexual	148	20	168	2.587	1.589	4.212	**<0.001**
All other	759	266	1025				
IDU	389	177	575	0.476	0.362	0.625	**<0.001**
All other	509	109	618				
IDU/MSM	*	*	16	0.398	0.147	1.080	**<0.061**
All other	898	279	1177				
MSM	303	57	360	2.055	1.487	2.839	**<0.001**
All other	604	229	833				
mother to child (vertical)	*	*	13	1.739	0.383	7.893	**<0.468**
All other	896	284	1180				

Those with greatest odds of dying with an AIDS diagnosis were those infected with HIV through the heterosexual route, MSM and mother to child (vertical) transmission were next. These were statistically significantly more likely to die with an AIDS diagnosis than others, while those who were infected through haemophilia or IDU were statistically significantly less likely to die with AIDS (see table).

Hepatitis

Similarly the odds for dying with any hepatitis diagnosis for each risk (transmission) group in comparison to other HIV+ people is shown in table 8.9

Table 8.9 OR for any hepatitis (any COD position) by risk group

Risk group	Hepatitis n=85	No hepatitis n=1106	Total N=1191	OR for having hepatitis	95% CL lower	95% CL upper	P for χ^2
Blood/tissue	*	*	18	1.642	0.371	7.261	**n/a**
All other	83	1092	1175				
Haemophilia	*	*	35	0.783	0.185	3.322	**n/a**
All other	83	1075	1158				
Heterosexual	*	*	168	0.362	0.144	0.906	**<0.034**
All other	80	945	1025				
IDU	69	506	575	5.132	2.942	8.954	**<0.001**
All other	16	602	618				
IDU/MSM	*	*	16	1.88	0.420	8.409	**n/a**
All other	83	1094	1177				
MSM	*	*	360	0.133	0.053	0.331	**<0.001**
All other	80	753	833				
mother to child (vertical)	0	13	13	-	-	-	**n/a**
All other	85	1095	1180				

Those with greatest odds of dying with a hepatitis diagnosis were those infected with HIV through the IDU or IDU/MSM routes, blood/tissue transmission was next, but for only IDU were there sufficient expected cases to allow calculation of a significance for Chi square. The CI is quite wide for IDUs, but is above one and a long way from including one. For heterosexuals the CI is narrow, below one, but quite close to one. Heterosexuals had 36% of the odds of death with hepatitis compared to all other transmission groups, and IDUs were statistically significantly more likely to die with a hepatitis diagnosis than other transmission groups (with over five times the odds). MSM and heterosexual people were statistically significantly less likely to die with a hepatitis diagnosis than others (see table 8.9).

Odds ratios for death by HAART era of first report

As a comparison with the unadjusted ORs from the logistic regression the OR for death pre-HAART compared to post-HAART was calculated (table 8.10). The odds of death pre-HAART were more than 19 times as great as post HAART. Early, late and ultra active HAART ORs were then calculated in reference to pre-HAART

Table 8.10 pre and post HAART comparisons of ORs for death

HAART era	Deceased (n=1593)	Alive (n=4280)	Total (n=5873)	OR for death	Lower 95% CL	Upper 95% CL	P for χ^2
Pre-HAART	1417	1261	2678	19.275	16.264	22.844	**<0.001**
Post HAART	176	3019	3195				
Early HAART	71	430	501	0.147	0.113	0.191	**<0.001**
Pre-HAART	1417	1261	2678				
Late HAART	58	810	868	0.064	0.048	0.084	**<0.001**
Pre-HAART	1417	1261	2678				
Ultra-active HAART	47	1779	1826	0.024	0.017	0.032	**<0.001**
Pre-HAART	1417	1261	2678				

9. Life Expectancy

A current complete life table giving number of years' life expectancy after first report was created and stratified by age group at diagnosis for the year 2008. It is presented here. There were 31 deaths in that year. A current complete life table for life expectancy was also created by year of age at 31.12.2008, and stratified by age group at diagnosis. That is included in Appendix 7 for better comparison with other studies found in the literature review.

The life expectancy from first report was 15.3 years for those aged 0-19 at first report, 13.3 years for those aged 20-24, 10.1 for those 25-34, 7.6 for those 35-44 and 6.6 for those 45+. These are mean years of life left for all the people in that age range. The life expectancy for each year of age was greater than these figures might suggest (see table in appendix 7), because as people died the remaining years of life were distributed among fewer people.

From the current complete life table overall, not stratified by age group at first report, (see appendix 7) the life expectancy by year of current age at 31.12.2008 was 22.9 years at age 20, reducing to 7.9 years at age 45, and two years for the one person aged 83.

Table 9.1 Current complete life table for the year 2008: number of years' life expectancy after first report stratified by age group at first report

Age group 0-19: Years of life expectancy from HIV initial first report to death or 31.12.08

(yrs following first report to 25/9/09 or death in 1981-2009) Interval Start Time	(Pop) Number Entering Interval	(Censored - live at 25.9.09) Number Withdrawing during Interval	lx Number Exposed to Risk	dx Number of Terminal Events (Deaths)	qx (=dx-lx) Proportion Terminating	px (=1-qx) Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Lx (Pop - deaths) + half deaths	Tx (cumulative years lived by those over that time)	ex (Mean additional years to be lived at that time)
0	228	5	225.500	1	.00	1.00	1.00	.00	227.5	3452.5	**15.31**
1	222	15	214.500	0	.00	1.00	1.00	.00	222	3225	**15.03**
2	207	6	204.000	0	.00	1.00	1.00	.00	207	3003	**14.72**
3	201	6	198.000	0	.00	1.00	1.00	.00	201	2796	**14.12**
4	195	16	187.000	0	.00	1.00	1.00	.00	195	2595	**13.88**
5	179	9	174.500	0	.00	1.00	1.00	.00	179	2400	**13.75**
6	170	4	168.000	0	.00	1.00	1.00	.00	170	2221	**13.22**
7	166	10	161.000	0	.00	1.00	1.00	.00	166	2051	**12.74**
8	156	6	153.000	0	.00	1.00	1.00	.00	156	1885	**12.32**
9	150	9	145.500	0	.00	1.00	1.00	.00	150	1729	**11.88**
10	141	1	140.500	0	.00	1.00	1.00	.00	141	1579	**11.24**
11	140	9	135.500	0	.00	1.00	1.00	.00	140	1438	**10.61**
12	131	2	130.000	0	.00	1.00	1.00	.00	131	1298	**9.98**
13	129	2	128.000	0	.00	1.00	1.00	.00	129	1167	**9.12**
14	127	7	123.500	0	.00	1.00	1.00	.00	127	1038	**8.40**
15	120	8	116.000	0	.00	1.00	1.00	.00	120	911	**7.85**
16	112	3	110.500	0	.00	1.00	1.00	.00	112	791	**7.16**
17	109	7	105.500	0	.00	1.00	1.00	.00	109	679	**6.44**
18	102	5	99.500	0	.00	1.00	1.00	.00	102	570	**5.73**
19	97	7	93.500	0	.00	1.00	1.00	.00	97	468	**5.01**
20	90	5	87.500	0	.00	1.00	1.00	.00	90	371	**4.24**
21	85	8	81.000	0	.00	1.00	1.00	.00	85	281	**3.47**
22	77	12	71.000	0	.00	1.00	1.00	.00	77	196	**2.76**
23	65	29	50.500	0	.00	1.00	1.00	.00	65	119	**2.36**
24	36	23	24.500	0	.00	1.00	1.00	.00	36	54	**2.20**
25	13	8	9.000	0	.00	1.00	1.00	.00	13	18	**2.00**
26	5	5	2.500	0	.00	1.00	1.00	.00	5	5	**2.00**

Age group 20-24: Years of life expectancy from HIV initial first report to death or 31.12.08

(yrs following first report to 25/9/09 or death in 1981-2009) Interval Start Time	(Pop) Number Entering Interval	(Censored - live at 25.9.09) Number Withdrawing during Interval	lx Number Exposed to Risk	dx Number of Terminal Events (Deaths)	qx (=dx-lx) Proportion Terminating	px (=1-qx) Proportion Surviving	Cumulative Px (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Lx (Pop - deaths) + half deaths	Tx (cumulative years lived by those over that time)	ex (Mean additional years to be lived at that time)
0	604	19	594.500	0	.00	1.00	1.00	.00	604	7879	**13.25**
1	585	43	563.500	0	.00	1.00	1.00	.00	585	7275	**12.91**
2	542	25	529.500	0	.00	1.00	1.00	.00	542	6690	**12.63**
3	517	41	496.500	0	.00	1.00	1.00	.00	517	6148	**12.38**
4	476	45	453.500	0	.00	1.00	1.00	.00	476	5631	**12.42**
5	431	38	412.000	0	.00	1.00	1.00	.00	431	5155	**12.51**
6	393	20	383.000	0	.00	1.00	1.00	.00	393	4724	**12.33**
7	373	18	364.000	0	.00	1.00	1.00	.00	373	4331	**11.90**
8	355	15	347.500	0	.00	1.00	1.00	.00	355	3958	**11.39**
9	340	13	333.500	0	.00	1.00	1.00	.00	340	3603	**10.80**
10	327	14	320.000	0	.00	1.00	1.00	.00	327	3263	**10.20**
11	313	10	308.000	1	.00	1.00	1.00	.00	312.5	2936	**9.53**
12	302	20	292.000	0	.00	1.00	1.00	.00	302	2623.5	**8.98**
13	282	5	279.500	0	.00	1.00	1.00	.00	282	2321.5	**8.31**
14	277	12	271.000	0	.00	1.00	1.00	.00	277	2039.5	**7.53**
15	265	23	253.500	0	.00	1.00	1.00	.00	265	1762.5	**6.95**
16	242	14	235.000	1	.00	1.00	.99	.01	241.5	1497.5	**6.37**
17	227	15	219.500	0	.00	1.00	.99	.01	227	1256	**5.72**
18	212	12	206.000	0	.00	1.00	.99	.01	212	1029	**5.00**
19	200	19	190.500	0	.00	1.00	.99	.01	200	817	**4.29**
20	181	12	175.000	0	.00	1.00	.99	.01	181	617	**3.53**
21	169	43	147.500	0	.00	1.00	.99	.01	169	436	**2.96**
22	126	38	107.000	1	.01	.99	.98	.01	125.5	267	**2.50**
23	87	40	67.000	1	.01	.99	.97	.02	86.5	141.5	**2.11**
24	46	38	27.000	0	.00	1.00	.97	.02	46	55	**2.04**
25	8	7	4.500	0	.00	1.00	.97	.02	8	9	**2.00**
26	1	1	.500	0	.00	1.00	.97	.02	1	1	**2.00**

Age group 25-34: Years of life expectancy from HIV initial first report to death or 31.12.08

(yrs following first report to 25/9/09 or death in 1981-2009) Interval Start Time	(Pop) Number Entering Interval	(Censored - live at 25.9.09) Number Withdrawing during Interval	lx Number Exposed to Risk	dx Number of Terminal Events (Deaths)	qx (=dx-lx) Proportion Terminating	px (=1-qx) Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Lx (Pop - deaths) + half deaths	Tx (cumulative years lived by those over that time)	ex (Mean additional years to be lived at that time)
0	1777	134	1710.000	2	.00	1.00	1.00	.00	1776	17227	**10.07**
1	1641	145	1568.500	1	.00	1.00	1.00	.00	1640.5	15451	**9.85**
2	1495	108	1441.000	1	.00	1.00	1.00	.00	1494.5	13810.5	**9.58**
3	1386	130	1321.000	1	.00	1.00	1.00	.00	1385.5	12316	**9.32**
4	1255	127	1191.500	0	.00	1.00	1.00	.00	1255	10930.5	**9.17**
5	1128	109	1073.500	0	.00	1.00	1.00	.00	1128	9675.5	**9.01**
6	1019	88	975.000	0	.00	1.00	1.00	.00	1019	8547.5	**8.77**
7	931	75	893.500	0	.00	1.00	1.00	.00	931	7528.5	**8.43**
8	856	65	823.500	0	.00	1.00	1.00	.00	856	6597.5	**8.01**
9	791	70	756.000	0	.00	1.00	1.00	.00	791	5741.5	**7.59**
10	721	71	685.500	2	.00	1.00	.99	.00	720	4950.5	**7.22**
11	648	63	616.500	1	.00	1.00	.99	.00	647.5	4230.5	**6.86**
12	584	60	554.000	0	.00	1.00	.99	.00	584	3583	**6.47**
13	524	68	490.000	0	.00	1.00	.99	.00	524	2999	**6.12**
14	456	64	424.000	1	.00	1.00	.99	.00	455.5	2475	**5.84**
15	391	56	363.000	1	.00	1.00	.99	.00	390.5	2019.5	**5.56**
16	334	46	311.000	2	.01	.99	.98	.01	333	1629	**5.24**
17	286	44	264.000	0	.00	1.00	.98	.01	286	1296	**4.91**
18	242	29	227.500	0	.00	1.00	.98	.01	242	1010	**4.44**
19	213	26	200.000	0	.00	1.00	.98	.01	213	768	**3.84**
20	187	32	171.000	0	.00	1.00	.98	.01	187	555	**3.25**
21	155	39	135.500	0	.00	1.00	.98	.01	155	368	**2.72**
22	116	48	92.000	0	.00	1.00	.98	.01	116	213	**2.32**
23	68	46	45.000	0	.00	1.00	.98	.01	68	97	**2.16**
24	22	18	13.000	0	.00	1.00	.98	.01	22	29	**2.23**
25	4	2	3.000	0	.00	1.00	.98	.01	4	7	**2.33**
26	2	1	1.500	0	.00	1.00	.98	.01	2	3	**2.00**
27	1	1	.500	0	.00	1.00	.98	.01	1	1	**2.00**

Age group 35-44: Years of life expectancy from HIV initial first report to death or 31.12.08

(yrs following first report to 25/9/09 or death in 1981-2009) Interval Start Time	(Pop) Number Entering Interval	(Censored - live at 25.9.09) Number Withdrawing during Interval	lx Number Exposed to Risk	dx Number of Terminal Events (Deaths)	qx (=dx-lx) Proportion Terminating	px (=1-qx) Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Lx (Pop - deaths) + half deaths	Tx (cumulative years lived by those over that time)	ex (Mean additional years to be lived at that time)
0	1129	102	1078.000	0	.00	1.00	1.00	.00	1129	8158.5	**7.57**
1	1027	125	964.500	0	.00	1.00	1.00	.00	1027	7029.5	**7.29**
2	902	105	849.500	1	.00	1.00	1.00	.00	901.5	6002.5	**7.07**
3	796	115	738.500	0	.00	1.00	1.00	.00	796	5101	**6.91**
4	681	109	626.500	0	.00	1.00	1.00	.00	681	4305	**6.87**
5	572	76	534.000	0	.00	1.00	1.00	.00	572	3624	**6.79**
6	496	71	460.500	0	.00	1.00	1.00	.00	496	3052	**6.63**
7	425	53	398.500	0	.00	1.00	1.00	.00	425	2556	**6.41**
8	372	45	349.500	1	.00	1.00	1.00	.00	371.5	2131	**6.10**
9	326	37	307.500	1	.00	1.00	.99	.00	325.5	1759.5	**5.72**
10	288	47	264.500	2	.01	.99	.99	.01	287	1434	**5.42**
11	239	40	219.000	0	.00	1.00	.99	.01	239	1147	**5.24**
12	199	37	180.500	0	.00	1.00	.99	.01	199	908	**5.03**
13	162	33	145.500	0	.00	1.00	.99	.01	162	709	**4.87**
14	129	23	117.500	1	.01	.99	.98	.01	128.5	547	**4.66**
15	105	23	93.500	1	.01	.99	.97	.01	104.5	418.5	**4.48**
16	81	14	74.000	0	.00	1.00	.97	.01	81	314	**4.24**
17	67	18	58.000	0	.00	1.00	.97	.01	67	233	**4.02**
18	49	10	44.000	2	.05	.95	.92	.03	48	166	**3.77**
19	37	5	34.500	0	.00	1.00	.92	.03	37	118	**3.42**
20	32	10	27.000	0	.00	1.00	.92	.03	32	81	**3.00**
21	22	7	18.500	0	.00	1.00	.92	.03	22	49	**2.65**
22	15	7	11.500	0	.00	1.00	.92	.03	15	27	**2.35**
23	8	4	6.000	0	.00	1.00	.92	.03	8	12	**2.00**
24	4	4	2.000	0	.00	1.00	.92	.03	4	4	**2.00**

Age group 45+ Years of life expectancy from HIV initial first report to death or 31.12.08

(yrs following first report to 25/9/09 or death in 1981-2009) Interval Start Time	(Pop) Number Entering Interval	(Censored - live at 25.9.09) Number Withdrawing during Interval	lx Number Exposed to Risk	dx Number of Terminal Events (Deaths)	qx (=dx-lx) Proportion Terminating	px (=1-qx) Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Lx (Pop - deaths) + half deaths	Tx (cumulative years lived by those over that time)	ex (Mean additional years to be lived at that time)
0	497	58	468.000	2	.00	1.00	1.00	.00	496	3079.5	**6.58**
1	437	42	416.000	0	.00	1.00	1.00	.00	437	2583.5	**6.21**
2	395	54	368.000	1	.00	1.00	.99	.00	394.5	2146.5	**5.83**
3	340	68	306.000	0	.00	1.00	.99	.00	340	1752	**5.73**
4	272	58	243.000	1	.00	1.00	.99	.01	271.5	1412	**5.81**
5	213	42	192.000	0	.00	1.00	.99	.01	213	1140.5	**5.94**
6	171	31	155.500	0	.00	1.00	.99	.01	171	927.5	**5.96**
7	140	22	129.000	0	.00	1.00	.99	.01	140	756.5	**5.86**
8	118	14	111.000	0	.00	1.00	.99	.01	118	616.5	**5.55**
9	104	16	96.000	0	.00	1.00	.99	.01	104	498.5	**5.19**
10	88	16	80.000	0	.00	1.00	.99	.01	88	394.5	**4.93**
11	72	14	65.000	0	.00	1.00	.99	.01	72	306.5	**4.72**
12	58	14	51.000	0	.00	1.00	.99	.01	58	234.5	**4.60**
13	44	14	37.000	1	.03	.97	.96	.03	43.5	176.5	**4.77**
14	29	6	26.000	0	.00	1.00	.96	.03	29	133	**5.12**
15	23	2	22.000	0	.00	1.00	.96	.03	23	104	**4.73**
16	21	3	19.500	0	.00	1.00	.96	.03	21	81	**4.15**
17	18	5	15.500	0	.00	1.00	.96	.03	18	60	**3.87**
18	13	3	11.500	0	.00	1.00	.96	.03	13	42	**3.65**
19	10	1	9.500	0	.00	1.00	.96	.03	10	29	**3.05**
20	9	4	7.000	0	.00	1.00	.96	.03	9	19	**2.71**
21	5	1	4.500	0	.00	1.00	.96	.03	5	10	**2.22**
22	4	3	2.500	0	.00	1.00	.96	.03	4	5	**2.00**
23	1	1	.500	0	.00	1.00	.96	.03	1	1	**2.00**

10. Deaths grouped by primary cause of death (classified within AIDS defining or not) and by HAART era of first report

10.1 Overall proportions within the sample

The coded AIDS defining COD groups were as shown in Fig 10.1 and table 10.1 for the primary COD.[f] This is 'death from AIDS', and is not the same as death with an AIDS defining diagnosis in any position ('death with AIDS').

Fig 10.1 AIDS defining groups for primary COD by era of HAART first report

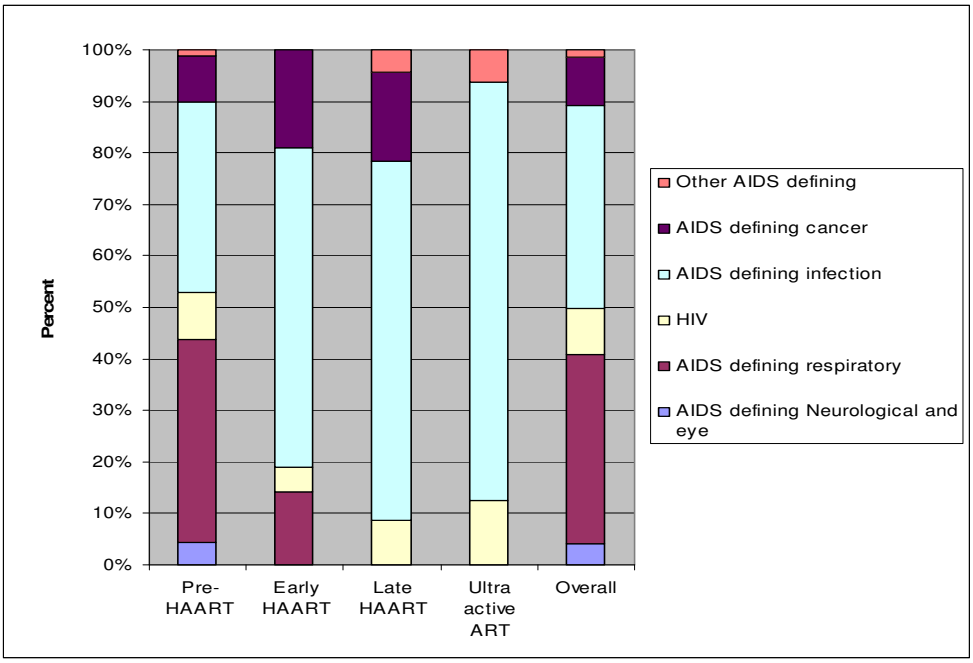


Table 10.1 AIDS defining groups for primary COD by era of HAART first report

	Pre-HAART	Early HAART	Late HAART	Ultra active ART	Overall
AIDS defining respiratory	39.4%	14.3%	0%	0%	**36.7%**
AIDS defining infection	37.0%	61.9%	69.6%	81.3%	**39.6%**
HIV	8.9%	4.8%	8.7%	12.5%	**8.9%**
AIDS defining cancer	8.9%	19.1%	17.4%	0%	**9.3%**
AIDS defining Neurological and eye	4.4%	0%	0%	0%	**4.1%**
Other AIDS defining	1.3%	0%	4.4%	6.3%	**1.4%**
Total N (all AIDS)	**705**	**21**	**23**	**16**	**765**

[f] Note 'death with AIDS' means AIDS as any cause of death, 'death from AIDS', means AIDS as the primary cause of death.

The numbers in each of the main categories pre-HAART were small in the post HAART eras, but AIDS defining infections increasingly dominated as a percentage of the AIDS deaths. A full breakdown of primary causes of death by grouping within the AIDS and non AIDS categories is given in appendix 6.

The main non AIDS defining COD groups by era of HAART and primary COD were as shown in Fig 10.2 and table 10.2. Again the complete list of all diagnostic groups (by whether or not AIDS defining) is given in appendix 6, some are combined for the purposes of the graph. There was a large reduction in all the groups. Cancer and cardiovascular causes featured in the two latest eras. Suicide reduced to zero post HAART.

Fig 10.2 Non-AIDS defining groups for primary COD by era of HAART first report

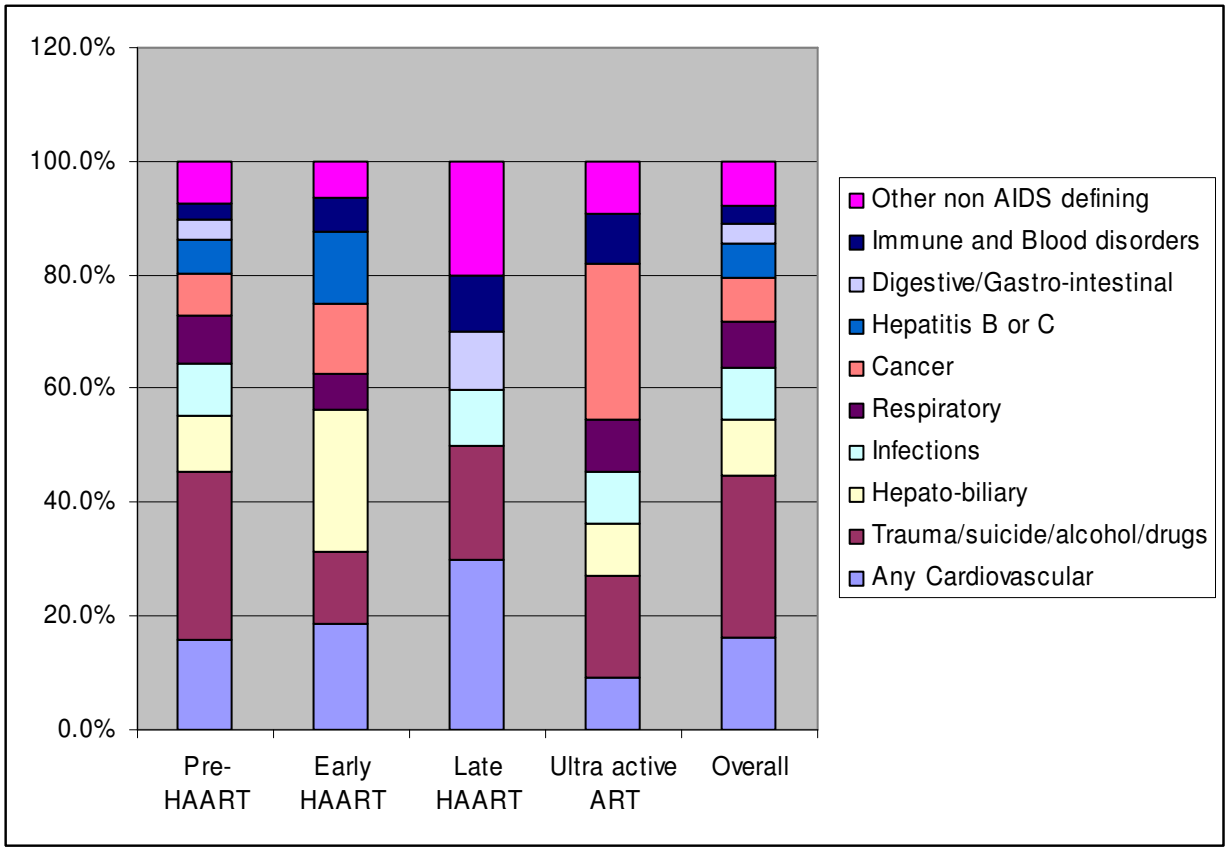


Table 10.2 Non-AIDS defining groups for primary COD by era of HAART first report

	Pre-HAART	Early HAART	Late HAART	Ultra active ART	Overall
Trauma/suicide/alcohol/drugs	29.6%	12.5%	20.0%	18.2%	**28.4%**
Any Cardiovascular	15.9%	18.8%	30.0%	9.1%	**16.2%**
Hepato-biliary	9.8%	25.0%	0.0%	9.1%	**10.1%**
Infections	9.3%	0.0%	10.0%	9.1%	**8.9%**
Respiratory	8.5%	6.3%	0.0%	9.1%	**8.2%**
Other non AIDS defining	7.5%	6.3%	20.0%	9.1%	**7.7%**
Cancer	7.2%	12.5%	0.0%	27.3%	**7.7%**
Hepatitis B or C	6.2%	12.5%	0.0%	0.0%	**6.1%**
Digestive/Gastro-intestinal	3.3%	0.0%	10.0%	0.0%	**3.3%**
Immune and Blood disorders	2.8%	6.3%	10.0%	9.1%	**3.3%**
Total N (all non-AIDS)	**389**	**16**	**10**	**11**	**426**

The proportion of deaths that were from AIDS (i.e. Primary cause was an AIDS defining COD) did not decrease over the four eras at a statistically significant level (table 10.3). Over the latest three eras the change for death from AIDS as primary cause was also not statistically significant (chi square for trend <0.760).

Table 10.3 Proportion of AIDS defining and non AIDS defining primary cause of death by HAART era.

Whether Primary COD was AIDS defining	Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra active ART (%)	Total (%)	p for $\mathcal{X}^2$ for trend
AIDS defining	705 (64.4)	21 (56.8)	23 (69.7)	16 (59.3)	**765 (64.2)**	**<0.734**
Not AIDS defining	389 (35.6)	16 (43.2)	10 (30.3)	11 (40.7)	**426 (35.8)**	
Total	**1094 (100)**	**37 (100)**	**33 (100)**	**27 (100)**	**1191 (100)**	

Note: 402 cases with missing COD are excluded

Although this section focuses on primary COD, the proportion of deaths with AIDS (AIDS defining cause of death in any position) is reported (table 10.4) because, in contrast to primary COD AIDS, it increased over the four eras at a statistically significant level (table 10.4). Over the last three eras only, the change was not statistically significant for death with AIDS as any cause ($\mathcal{X}^2$ for trend for p<0.184).

Table 10.4 proportions that were death with AIDS (any COD) by era of first report

Whether the patient had an AIDS COD (any position)	Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra-active HAART (%)	Total (%)	p for $\mathcal{X}^2$ for trend
AIDS	818 (74.8)	31 (83.8)	32 (97)	25 (92.6)	**906 (76.1)**	**<0.001**
Not AIDS	276 (25.2)	* (16.2)	* (3)	* (7.4)	**285**	
Total	**1094 (100)**	**37 (100)**	**33 (100)**	**27 (100)**	**1191 (100)**	

Note: the numbers in table 10.4 for AIDS and non-AIDS (any COD) are different from the primary cause analysis (table 10.3) above. As for table 10.3, 402 cases with missing COD are excluded. See appendix 13 for tables including COD unknown.

An age analysis on primary cause of death was carried out to compare the mean age of patients who would die (not had already died) and who had reported by the 30th June in a chosen year (table 10.5 below). The year chosen was at a midpoint in each era (except two dates were taken in the ultra-active HAART era). Note the age was age at the 30th June in each year, and not age at first report.

Table 10.5 Mean age in years at 30 June in each year of prevalent patients by whether AIDS was the primary cause of death or not.**

Whether the patient had an AIDS COD as primary cause	30.6.1989		30.6.1998		30.6.2001		30.6.2004		30.6.2007		
	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	**Total**
AIDS	29.81	207	37.5	92	40.39	66	43.36	35	41.71	8	**408**
Not AIDS	30.39	340	36.78	120	39.93	72	45.14	30	49.56	1	**563**
COD unknown	29.93	168	38.79	97	40.7	70	43.45	34	45.49	24	**393**
Overall	**30.11**	**715**	**37.63**	**309**	**40.33**	**208**	**43.93**	**99**	**44.7**	**33**	**1364**

** referred by then and alive then, but who died by 25.9.2009

There was only one non-AIDS death after 30 June 2007, and there were no deaths after 30.3.2009. Patients who died before 30.6.1989 or were referred after 30.6.2007 are excluded because not part of the prevalent population at any of the chosen dates. The final column counts occurrences not people as the same person could be alive and part of the prevalent population at multiple dates. The SPSS syntax for this analysis is given in appendix 10. There was an increasing trend in mean age for both groups up to 2004. There was a small drop for those dying with an AIDS cause after 2007, but only one non-AIDS death was involved at 2007.

10.2 Survival time to death from AIDS (primary cause) or death with hepatitis (any cause) by HAART era of first report

AIDS

Changes in survival time from first HIV report to death among those with any AIDS diagnosis at death were further assessed by HAART era of first report.

The method for this was as follows, for the full data file of 5873 cases:

1. The cases of interest were those with an AIDS defining COD as the primary cause of death. Those with COD unknown, or who died without an AIDS defining COD were censored. SPSS treated the cases still alive at 25.9.09 as missing since they had no COD.
2. Era of first report was entered as the Factor.

The Kaplan Meier survival curve is shown in Fig 10.3 below. It shows better survival times for people dying of AIDS for those first reporting pre-HAART than for those reporting post-HAART. Caplan 1994[155] discusses the limitations of Kaplan-Meier curves in situations of competing risks such as the one described. See the foot note below.[g]

Hepatitis

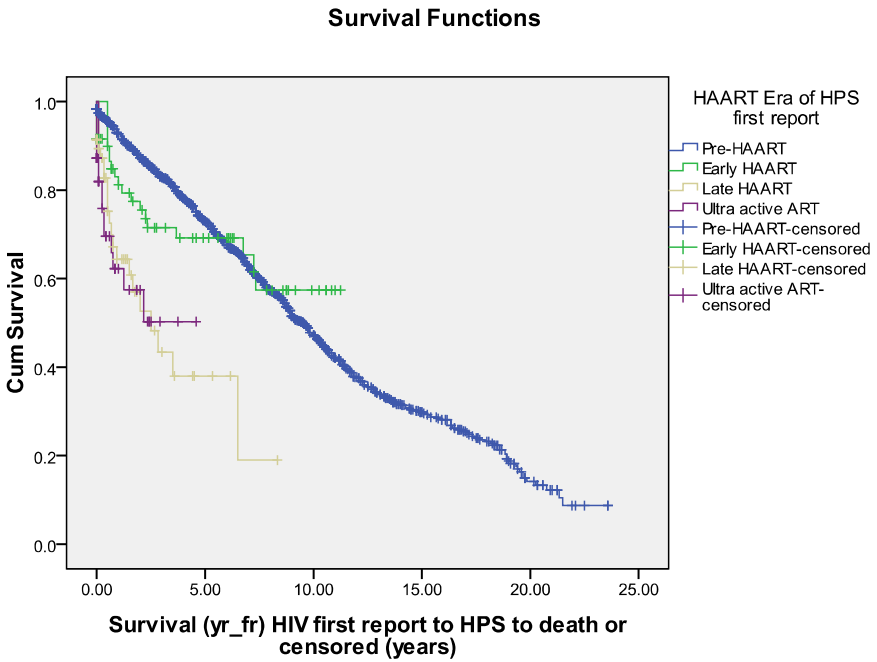
Hepatitis as any cause was used here because there were very low numbers with hepatitis as a primary cause of death. The method for this was as follows, for the full data file of 5873 cases:

1. The cases of interest were those with any hepatitis COD (Hepatitis B, Hepatitis C or Hepatitis unspecified). Those with COD unknown, or who died without any hepatitis COD were censored. SPSS treated the cases still alive at 25.9.09 as missing since they had no COD.
2. Era of first report was entered as the Factor.

The Kaplan Meier survival curve is shown in figure 10.4 alongside the survival curve for AIDS defining primary COD. It shows better survival times than for death from AIDS, but somewhat worse survival time than pre-HAART for hepatitis for those first reporting in early and late HAART, but the hepatitis curve for those reporting in the ultra-active HAART period looks very close to the pre-HAART hepatitis curve. There were, however, small numbers of deaths with any hepatitis in people who first reported post HAART. Figures were: 80 in pre-HAART, 4 in early HAART, 1 in late HAART, and none in ultra-active HAART.

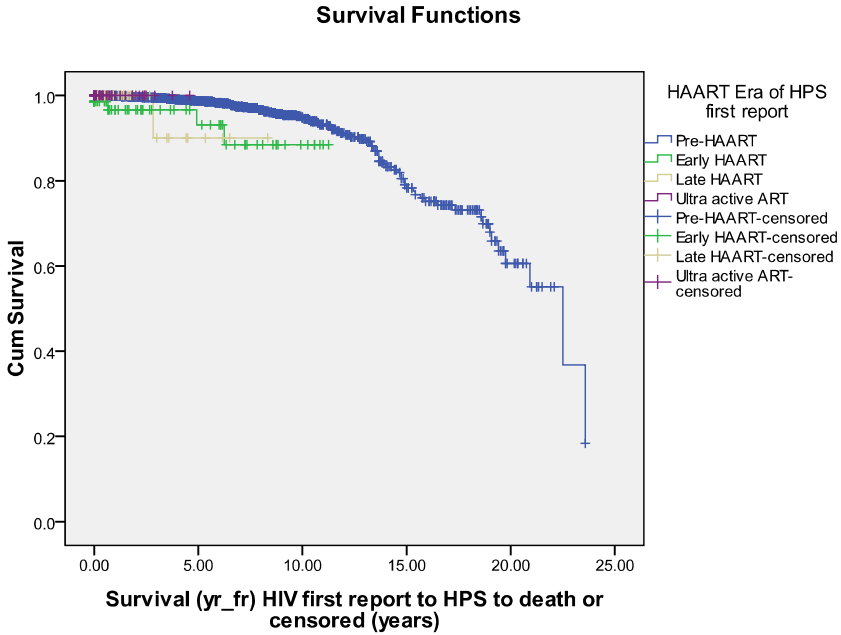
[g] "Kaplan-Meier curves overestimate the probability of late complications when there is a high mortality rate. Cumulative incidence and cumulative conditional probability accurately give the probability and risk of cause-specific failure. "Caplan 1994.

Fig 10.3 Survival (1st report to death or censored) for people dying of AIDS (primary cause) compared by HAART era of first report



(Log rank p<0.001)

Fig 10.4 Survival (1st report to death or censored) for people dying with any form of hepatitis as any cause compared by HAART era of first report



Log rank p<0.03

The survival plot for AIDS defining diagnoses as any cause of death is not shown since this section focuses on primary COD. AIDS defining diagnoses as any COD displayed a survival pattern by era similar to AIDS as primary COD, but with more clearly separated curves showing decreasing survival time from pre-HAART to ultra-active HAART in each era of first report.

Cox's hazard ratios were run for equivalent models as those shown for the survival plots above, i.e. for AIDS, death with an AIDS defining primary COD was the event of interest, cases not dying with an AIDS defining primary COD or COD unknown were censored, and era of first report was entered as a covariate with era 1 as the reference category. This gave an increasing hazard of death from AIDS in all post-HAART eras in comparison to the pre- HAART era, compared to death from other causes (including COD unknown). The Cox's hazard ratios are shown in table 10.6 below:

Table 10.6 Hazard ratios for death from AIDS (AIDS as primary cause) by era of HAART

Comparison	Hazard Ratio for death, from Cox Proportional hazards model	95.0% CI for Hazard ratio		Sig.
		Lower	Upper	
Difference for HAART eras overall				**.000**
Early HAART compared to pre-HAART	1.093	.707	1.689	**.690**
Late HAART compared to pre-HAART	3.818	2.498	5.837	**.000**
Ultra-active HAART compared to pre-HAART	4.690	2.817	7.807	**.000**

LML plots were satisfactory (parallel lines).

So, compared to pre-HAART, post HAART there was an increased hazard of death from AIDS for those who died. For those who died, survival time was lower post HAART for those who died of AIDS, and, for those who died, the hazard of death from AIDS increased over the three post HAART eras of first report. For death with AIDS as any COD a similar analysis (not shown) gave a similar pattern of increasing hazard ratios, but with larger hazard ratios in comparison to pre-HAART.

For the Cox's hazard ratios for any hepatitis COD, again, similarly to the procedure for AIDS, an equivalent Cox's hazards regression model was run to the hepatitis survival plot (table 10.7). That gave statistically significantly decreasing hazards over the eras of first report for dying with any hepatitis (these were mainly co-morbid hepatitis).

Table 10.7 Hazard ratios for death with any hepatitis in comparison to pre-HAART by era of HAART

Comparison	Hazard Ratio for death, from Cox Proportional hazards model	95.0% CI for Hazard ratio		Sig.
		Lower	Upper	
Difference for HAART eras overall				**.000**
Early HAART compared to pre-HAART	.274	.216	.349	**.000**
Late HAART compared to pre-HAART	.180	.138	.234	**.000**
Ultra-active HAART compared to pre-HAART	.140	.104	.188	**.000**

Thus for those who died, hazard of death from AIDS increased, while hazard of death with hepatitis decreased. The above analysis can be contrasted with the reducing risk of death overall (not just from AIDS) which was demonstrated for five year survival data in the survival time section. Overall survival time showed hazard reducing similarly to five year survival over the eras (table 10.8), but hazard ratios were slightly lower for overall compared to five year survival:

Table 10.8 Hazard ratios for overall survival time (all deaths) by era of HAART from Cox's regression

Comparison	Hazard Ratio for death, from Cox Proportional hazards model	95.0% CI for Hazard ratio		Sig.
		Lower	Upper	
Difference for HAART eras overall	-	-	-	**0.001**
Early HAART compared to pre-HAART	.274	.216	.349	**0.001**
Late HAART compared to pre-HAART	.180	.138	.234	**0.001**
Ultra-active HAART compared to pre-HAART	.140	.104	.188	**0.001**

Table 10.8 above gives results from the Cox regression. LML plots were satisfactory. The Binomial logistic regression (reported previously) gave a confirmatory results pattern and is shown again below for comparison (table 10.9):

Table 10.9 Odds ratios for overall survival time (all deaths) by era of HAART from Binomial regression

Comparison	Odds ratio	95.0% CI for Odds ratio		Sig.
		Lower	Upper	
Difference for HAART eras overall	-	-	-	**0.001**
Early HAART compared to pre-HAART	.147	.113	.191	**0.001**
Late HAART compared to pre-HAART	.064	.048	.084	**0.001**
Ultra-active HAART compared to pre-HAART	.024	.017	.032	**0.001**

A similar approach could be taken to analysing competing risks and survival time using Kaplan Meier plots for the other main groups of cause of death (any position), but there was insufficient time for that.

11. Discussion

11.1 Demography

The steepest declines in absolute numbers of deaths among people testing positive for HIV in Scotland occurred just after the introduction of ART. This accorded with results from other studies in other locations, e.g. the ART collaboration,[156] and Bhaskaran et al 2008.[157]

The trends for increasing mean age at first report in Scotland and mean age among still living patients over time suggested that as well as living longer with HIV, it could be possible that people were contracting HIV later in life, (an hypothesis supported by the wider literature).[109;114] That later transmission perhaps indicated that the aging Scottish population living with HIV were transmitting it to their age peers, suggesting a need for prevention work in older age groups applied in Scotland. People may also be waiting longer before requesting an HIV test, suggesting a need to encourage earlier request. The always increasing mean age, as well as the increasing numbers, on the HPS HIV database had implications for services beyond the specialist HIV services caring for them. This may have affected female patients increasingly as the proportion of patients who were female increased over HAART eras.

Of all the cases on the database a much higher percentage of the white patients were dead, but that was clearly related to the fact that a greater proportion of patients reporting pre-HAART and in earlier eras of HAART were white (table 5.11). An increasing proportion of patients on the database were from non-white ethnic backgrounds and had a lower hazard of death. This appeared to be opposite to trends identified in the wider research, which showed worse access to treatment,[26;158] more hardship,[159] more comorbidity[160] and worse outcomes[161] for non-white than white groups. Some of the non-white patients may have been migrants, possibly educational migrants whose stay in Scotland was of limited duration, so were not long term patients for the NHS. They may also have been protected by a better socio-economic context in their country of origin. As Arnold suggested,[162] ethnicity and deprivation can confound each other in AIDS survival. An increasing proportion

were heterosexual. Heterosexuals were largely exposed abroad. Any further service needs (capacity and type) analysis could assess the importance of these factors.

By transmission route, the highest proportion of cases who were deceased was among IDUs and haemophiliac people, as confirmed elsewhere for example Prins (2000).[163] A reduction in the proportion contracting HIV through this route was suggested elsewhere.[164] A reduction has also been reported elsewhere in the incidence of transmission to haemophiliac people following the introduction of viral inactivation steps for blood concentrates in 1986.[165] In the current study there was a statistically significant reduction in the proportion infected through the IDU and haemophilia routes across the eras of first report. A reduction in the mortality associated with IDUs was suggested in other literature.[166;167] There were statistically significant increases in the proportion infected through sexual contact (a slight increase for MSM and a much larger increase for heterosexual).

11.2 Mortality

Annual mortality fell from the introduction of HAART in 1996-1997, after peaking at 100/1000 in 1995. This strongly agrees with Crum's US finding that the annual death rate peaked at 103/1000 in 1995.[20]

SMR (the mortality standardised for age) for each sex showed the mortality rate in 2007 was only about a tenth in males of the mortality that would have been expected according to the mortality experience in 1989. There was a somewhat lower reduction in females (a lower reduction in female mortality was also found in a Canadian study.[168]) The SMR indicated a steeper reduction than shown in the crude annual mortality.

Although SMRs kept falling steeply after the introduction of HAART (see Figs 6.2 and 6.3) this was partly because of increasing numbers in the prevalent population with HIV, so not quite so positive as might appear from looking at the SMRs in the late and ultra-active HAART eras. Widely expressed concerns about comorbidity and treatment side effects among the increasing numbers living and aging with an HIV positive test result,[101] and the consequent implications for service use, therefore have relevance to Scotland.

The SMR trend using the Scottish 2001 population as reference showed a flattening off in the rate of fall. A Swiss study[169] found a seven-fold higher SMR pre-HAART in comparison to post-HAART for non IDU patients with a lower difference for IDU patients. They also found that women had a higher SMR than men both pre and post HAART. Our study found a greater than 25 fold higher SMR pre-HAART for women, and greater than 14 fold for men than in the ultra-active HAART period. The greater difference in comparison to the Swiss study can be explained by the different time periods used. The current study compared extreme ends of a wider range, the Swiss study compared only all pre-HAART from 1990-1995 to a truncated post-HAART for 1997-2001 only. The CIs for the SMRs in the current study were also wide in the pre-HAART era.

Limitations of mortality analysis

The flattening in the rate of fall in the current study with the 2001 general population as reference (compared to the 1989 HIV positive population as reference) could be owing to the broad age ranges I used, (0-19, 20-39, and 40+) which may not be sensitive to differences in expected deaths at higher ages, but that would need further analysis. A further limitation was the use of the 2001 Scottish population rather than the Scottish population for the same year as the HPS population at each time point, which may exaggerate the fall in SMR from 1989 to 1998, owing to likely higher mortality in the Scottish general population in 1989. However the pattern is likely to be similar enough in 1998-2007, as these years are closer to 2001, and the wide age ranges used are also likely to limit an effect from increasing life expectancy in the general population. SMR for HIV+ men in 2007 was lower than for the general population in 2001. In future as people with HIV populate particularly the 40+ age group at higher ages, in a distribution more similar to the general population, SMR calculated using the age groups used in the current study may be likely to increase owing to age effects.

Case ascertainment as an HIV death may not have been as complete in the HPS dataset in earlier eras. That would affect the SMRs, possibly reducing the SMR for the HPS HIV population in 1989, therefore making my estimates of effect err, but this time on the conservative side.

11.3 Survival time

Although they can adjust for different risks, mortality and binomial logistic regression analyses did not well reflect changes by era in survival times taking account of censored data. That was the reason for using special statistical methods for survival time analysis here to examine different risks individually. The survival time plots supported the more general literature. Five year as well as overall survival was plotted. Overall and five year survival times continued to improve with time, in accordance with findings that newer forms of HAART were associated with better survival time by Aracena (2008) et al.[170] HAART was not the only possible factor in the better survival time, and other covariates were investigated using logistic regression as discussed in the previous section. Hazard of death reduced in each era for the five year survival in comparison to pre-HAART.

Survival time for demographic variables confirmed that people who were older (45+) at first report had the lowest survival times in each era, men had statistically significantly lower survival times than females in all eras, black people had the best and white people the worst survival times, but statistically significant difference between all ethnic groups were confined to the pre- and early HAART periods, and for transmission groups, BTT had generally bad survival in each era, heterosexual had better survival in pre and early HAART, and IDU survival improved especially for those first reporting after the early HAART period, suggesting factors other than simply HAART may have been involved. Generally, except for BTT, the transmission groups converged towards better survival the later the era of first report.

Limitations

Possible limitations of the survival analysis include that censoring may not have been entirely random. Random censoring is a requirement of the log rank test.[149] Among those who had not been seen for over five years those aged 25-34 years at first report, were over represented. Reassuringly, there were no differences for sex or transmission group.

11.4 Risk factors over the eras – binomial logistic regression

In spite of the standardisation for age, the mortality analyses were not able to adjust for multiple possible confounding variables or assess the contribution of multiple causes to the survival outcome. The same held true for Kaplan Meier survival time analyses. That is why binomial logistic regression was used.

Overall adjusted odds ratios for death

A binomial logistic regression model including only era as a covariate gave the same unadjusted OR for death for each era as the ORs from simple crosstabulations. Unadjusted odds ratios for death overall were derived from simple cross tabulations of individual values of key categorical variables against all other values for that variable, without including era effects (tables 8.3-8.7) . They showed IDU's had the highest OR for death of all risk groups, (OR 5.5). This was in agreement with Sackoff (2006).[171] Those IDU's who died were also less likely than others who died to have AIDS in any COD position (OR 0.48, table 8.8) and more likely to have hepatitis (OR 5.1, table 8.9).

There were reduced odds ratios for HAART era of first report for adjusted ORs for death (table 7.2) as compared to the unadjusted ORs (table 7.1). In the final overall model there was, for each year of greater survival after first report, 13.2% of the OR for death compared to the previous year of survival. In general the literature suggested probability of death was linked to low CD4 count. For example latest CD4 count was the strongest predictor of disease progression in the US based Multicenter AIDS Cohort Study[172] and a Scottish study using lowest CD4 count agreed.[173] In addition, for AIDS defining malignancy, Monforte found:

> "a two-fold higher latest CD4 cell count was associated with a halving of the risk of ADM mortality"[174]

Part of the reduced hazard across eras in the current study was thus possibly related to increased earliest CD4 count, but a statistically significant drop in hazard over eras remained after adjustment for it.

Sackoff (2006)[175] found that a lowest CD4 count of below 50 was the strongest predictor of death. Lowest CD4 count was available for our study but earliest CD4 was chosen as the most likely to affect survival time.

Plausibly, HAART or other protective factors were now keeping people alive who first reported at lower CD4 counts. The literature supports that interpretation, for example Sabin 2006[12] found patients on HAART had a lower last median CD4 count before death than patients not on HAART. Connected to HAART there possibly may have been a double protective effect for these patients where, in the light of better prognosis, they were now less at risk from other factors (for example suicide and trauma), which could have resulted in death at higher CD4 counts.

For males there was a 2.3% greater adjusted OR for death than for females ($p<0.916$, table 7.2)). As it was statistically non significant, and as the 95% CI for the adjusted OR was quite tight (0.675-1.548) this may not mean that HIV+ males tended to be more vulnerable than HIV+ females, although that was suggested in the literature on hospital mortality.[176] The non-significant finding contrasted with the initial demographic analysis, where chi square for sex by whether alive or deceased was statistically significant overall (more men deceased) although there was no trend across eras for a higher proportion of dead patients to be men. The unadjusted OR (from table 8.4) for men was 1.74 (95% CI 1.52-2.0). Men were statistically significantly older at first report, which may explain why sex was not statistically significantly related to the adjusted OR for death in the final model. Other studies found women had higher mortality[19] High female mortality was also found, particularly in the pre and early HAART eras, in the current study – see the SMR figures (appendix 8). Lifestyle factors[21] and adherence to treatment, which were not adjusted for, may have been involved here.

Literature already discussed[111] suggests there were lower survival times and higher mortality rates five years after SC[177] for older people than the rate five years after SC for younger people. Although SC date was not known in our study, there was a 7.1% increase in adjusted odds of death for each year of age at first report compared to the previous year of age. That contrasted with a reduction for each year of age in unadjusted risk of 1.7%, since the unadjusted OR for age was 0.983 (0.977-0.988, $p<0.001$, HL test $p<0.001$).

White people had over five times greater OR for death than non white ($p<0.001$). This was lower than the unadjusted OR (from table 8.5) of 10.92 (8.5-14). The higher

white mortality was unexpected and appeared to contradict US studies which have found the opposite.[19;161] The authors suggested there was unequal access to HAART. A possible explanation was that the non-white population in Scotland differed from that in the US, with more reports from the non-white population in later eras when HAART was available to all.

People infected through the IDU route had statistically significantly lower adjusted OR for death than those infected through blood tissue transfers. The adjusted OR of death for IDUs in comparison to BTT was very small ($p<0.002$, table 7.2) whereas the unadjusted OR in comparison to BTT was greater (OR1.365, 0.775-2.402, $p<0.311$, appendix 12) although CI's were wide. The drop in adjusted compared to unadjusted OR might have been because death following transmission by IDU route, was strongly related to the factors adjusted for, including, era. The demographic analysis confirmed IDU transmission decreased through the eras for all (not just for deceased), and wider contextual knowledge of alcohol and drug harm prevention activities in Scotland over the period under review – e.g. needle exchange schemes,[178] also suggests this factor was important.

For both sexual transmission routes (heterosexual and MSM), the adjusted OR for death (referent to BTT, table 7.2) was statistically significantly lower than the referent transmission category of blood tissue transfer in this final model (adjusted OR MSM 0.005, $p<0.013$, Heterosexual, 0.012, $p<0.002$). These were lower than the unadjusted OR. For comparison the unadjusted ORs (referent to BTT – see appendix 12) were MSM 0.320, $p<0.001$, heterosexual 0.137, $p<0.001$). The percentage of cases by heterosexual transmission increased through the eras to over 50% in the ultra-active era, so numbers were sufficient to test. People with haemophilia (referent to BTT) had a statistically significantly lower adjusted OR (very small, $p<0.007$) compared to a statistically significantly higher unadjusted OR (1.333, $p<0.419$). Era effects are likely here, given the introduction of new blood screening procedures in 1986 as already mentioned.

Risk of death analysed by era of first report

The changing risk patterns according to the era of patient first report were analysed by stratifying the overall analysis, and including interactions if statistically significant within the era. The patterns are compared across eras here (table 11.1).

Table 11.1 Statistically significant risks of death by HAART era of first report

Pre-HAART	Early HAART	Late HAART	Ultra-active HAART
White ethnicity more likely to be dead. Transmission route (but none in particular in relation to BTT). Higher Earliest CD4 count less likely to be dead. Higher Age at first report less likely to be dead.	None – but model failed (see table 7.4 in results model 2c(ii) for adjusted odds of death).	MSM less likely to be dead.	IDU, other and unknown transmission categories less likely to be dead (in comparison to BTT). Higher Earliest CD4 count less likely to be dead.

Limitations

The binomial logistic regression for three of these analyses (late HAART was the exception) did not meet the requirements for the Hosmer –lemeshow test, so should be treated with caution.

Reasons for failure to meet data requirements, and resulting large confidence intervals were hinted at in the results, and the exact binomial logistic regression method[154] was a possible way forward. 'Exact' logistic regression techniques can deal with small numbers.[154]

Some examples of possible extra variables to include could be deprivation (SIMD), the drug history of each person, (which types of drugs and how long on them for), viral load count, clinic attended, social support, distance of home address from hospital, and any history of other comorbid conditions. These were generally not available in the dataset, but viral load count could have been included. Referent category choice was simple for the bivariate categorical variables, non white was chosen as this is used in the literature, females were chosen because the majority of HIV+ people are men, and BTT as they had the highest risk, so in comparison to BTT all others would be expressed as values below one making them easy to compare. Age and CD4 count were continuous so had no referent category.

11.5 Life expectancy

Some studies, including reviews[91;101] used the term 'life expectancy' to refer to a survival time analysis rather than a life table.[179] There are examples of life expectancy models for particular conditions (e.g. a Markov model for LE in CV disease[180]) being applied in HIV research to previously collected data to determine years of life saved by a particular treatment in comparison to another. Potential years of population life lost (PYLL) owing to the condition of concern can be calculated.[181] Keiser et al[169] calculated abridged life tables for the SWISS HIV cohort study for the range of years 1997-2001, and found life expectancy of 35.6 years at age 20-24. The figure of 49.4 years LE at age 20 (using mortality rates for 2003-2005) was given by the ART collaboration in their 2008 Lancet paper.[182] Lima et al[183] compared life expectancy at exact age 20 across four eras of therapy initiation, in British Columbia, Canada. In 1993-95 life expectancy was 9.1 years, 1996-98, 11.9 years, 1999-2001, 16.1 years, 2002-2004, 23.6 years.[184] Lohse et al, using lifetable methods, found an increase in median remaining lifetime from 8 years in 1995-6 to 33 years in 2000-05.[21;185]

The life expectancy in the current study given by the current complete life table by year of current age at 31.12.08 (appendix 7) was 22.9 years at age 20. This is much lower than some (but not all) of the figures given from the literature. With reference to the ART collaboration study in particular, reasons for this may include:

1. Their patients' analysis time started in 1996, whereas the analysis time in the current study includes patients still alive who first reported from 1981.
2. The current study includes patients from birth, theirs includes patients aged 16 and over.
3. Their study includes only patients who were ART naive and started on at least triple therapy, whereas the current includes all patients (who were alive in 2008). Aracena (2008) et al[186] found a sevenfold better life expectancy in patients on HAART compared to those not.
4. They used different methods to calculate life expectancy in abridged rather than complete life tables.
5. Rather than a single year they used deaths over a series of ranges of years (1996-1999, 2000-2002 and 2003-2005).

6. Life expectancy in Scotland in the HIV positive population may indeed be comparatively low. The lower LE could partly reflect the 'Scottish'[187] or 'Glasgow'[5;188] effects, and possibly associated dietary, alcohol, tobacco and drug use factors.

Thus the current life expectancy analysis reflects the actual life expectancies for the full group of people testing HIV positive rather than life expectancy for the highly selected group used by the ART. However, the small numbers of deaths in the single year 2008 and small sample size combined with use of the complete life table method may have affected the current results – see the life tables section in the methodological discussion below.

In the current study, the life expectancy from first report (table 9.1) was limited by the time available for survival after first report, a maximum of 27 years, and by the high mortality in the early years of HAART. Table 9.1 gives a comparison of life expectancies at differing numbers of years after first report for different age groups at first report. The clinical usefulness of this is that it shows life expectancy reduces both with age at first report and with number of years after first report in a regular fashion, and with no sudden changes in risk trajectory.

11.6 Causes of death

Cause of death groups

The stacked bars in the causes of death (figs 10.1.and 10.2) show varying proportions for different causes of death, but the numbers were small in the post HAART eras, limiting further discussion about changes in the broad groups of causes of death within the AIDS and non-AIDS categories over the post HAART eras. Primary cause of death was selected from all six COD positions and coding into groupings was rigorously checked. AIDS was coded using CDC definitions both from primary cause alone (death from AIDS) and, as a further validity test, from all causal positions (death with AIDS).

Crum[20] found AIDS defining causes of death (any position) declined from 79.7% pre-HAART (1990-1996) to 56% in the late HAART era (2000-2003). Figures in our study were 74.8% pre-HAART (1981-1996) and 97% late HAART (2000-2003). Our figures exclude COD unknown, which increased as a proportion of deaths by era (appendix

6). If COD unknown is included, there was a slight decrease from 57.7% pre-HAART to 53.2% in late HAART for death with AIDS (see appendix 13). These results and Crum's are not fully comparable also because Crum used era of death rather than era of first report. Era of first report was used here because it made a better link to treatment experienced from first report. There would be a time lag effect for death for the analysis by era of first report compared to analysis by era of death.

Although the current study did not distinguish HIV related deaths, (as distinct from AIDS deaths) the lack of a statistically significant downward trend in AIDS deaths (table 10.3) contrasted with Sackoff's (2006)[189] finding of a fall in HIV-related death from 1999-2004, although Sackoff's definition of HIV related is unclear. Like Crum, Sackoff used year of death in the cause of death analysis, which is difficult to compare with era of first report as used in the current study for the reasons described in the previous paragraph.

AIDS defining infection was the only AIDS-related cause of death in the ultra active HAART era of first report, continuing a trend evident in the preceding post-HAART eras, and in keeping with existing literature.[20] Tellez (2008)[190] reported a drop in the opportunistic infection Pneumocystis jiroveci pneumonia (PCP) from 52% pre-HAART to 37% in the HAART period. In the current study non-AIDS infections fell marginally as a proportion of all primary causes of death over a similar time period (see table 10.2 - from 9.3% pre-HAART to 9.1% of non-AIDS deaths in late HAART), and AIDS defining infections rose from 37% pre HAART to 69.6% of AIDS deaths in the late HAART era (see table 10.1). In the current study, AIDS defining respiratory infections fell from 39.4% (pre-HAART) to 0% in late HAART and non AIDS defining respiratory infection fell from 8.5% (pre-HAART) to 0%, in late HAART (table 10.1.).

The current results for non-AIDS-related deaths featured cardiovascular and cancer causes in the two later eras. Based on very small numbers, the proportion of deaths from non AIDS cancers increased from pre-HAART in patients first reporting in ultra-active HAART (table 10.2). D'Souza (2008) also found an increase in anal cancer incidence (a non-AIDS defining cancer) post-HAART. Bower 2005[47] noted a smaller improvement in prognosis for non-AIDS than for AIDS-defining cancers. In contrast, in the current study, although the proportion of deaths from AIDS defining cancers increased in patients first reporting in early and late HAART, it fell to zero in patients first reporting in ultra-active HAART. Falls post HAART in the incidence (Bahl 2008,[140] Bower 2006,[18] Gingues 2006,[46]) and proportion of deaths resulting from

AIDS defining cancers and events (Bonnet 2002,[17] Weber 2006[43]) have been widely reported elsewhere and linked to HAART (Battegay 2009[86]). Crum's 2006[20] finding that the proportion of all deaths that were from cancer peaked in 1996 accords with the current results suggesting the proportion of deaths fell post 1996 for AIDS-defining cancers but not for non-AIDS defining cancers.

The proportion of deaths from cardiovascular causes (all non-AIDS) increased in patients first reporting in late HAART but fell back in those first reporting in ultra-active HAART (table 10.2). Crum (2006)[20] found a statistically significant increase in the proportion of deaths with CV as any cause from 8.4% (51) pre-HAART to 21.8% (17) post HAART, so agreed partly with this (although her findings did not cover the ultra-active HAART era). Crum's primary cause analysis found eight CV deaths (9.6%) post HAART which was a statistically significant increase ($p<0.07$) compared to the pre HAART percentage (4.5%). Also in agreement with low CV incidence were Martinez 2009,[191] and Sackoff (2006)[192] who found in New York city that among persons with AIDS, for 1999-2004:

> "Mortality rates did not decrease significantly over time for the 3 leading non–HIV-related underlying causes of death (cardiovascular-, cancer-, and substance-related deaths) ($p> 0.100$)."

There were a few instances of HIV alone recorded as COD in the latest era. This could indicate a training issue for either doctors in completing death certificates or an issue for coders in coding deaths from information on death certificates.

Survival time with AIDS and with hepatitis

The survival analysis for COD focused on changes by era of first report in survival time among patients dying who had an AIDS-related COD as a primary or any cause (fig 10.3), and survival time in patients with any form of hepatitis in any position on the death certificate (fig 10.4).

The survival curves show worse survival for those dying from AIDS the later the era of HAART first report. Hepatitis survival time was worse for those first reporting in early and late HAART than pre-HAART but recovered in ultra-active HAART. Since,

although not shown, the any cause survival curves for AIDS were worse than the AIDS as primary cause survival it is clear from comparing the plots that survival time to death with an AIDS defining condition (in any position) was lower than survival time to death with any hepatitis condition in any position. It was initially expected hepatitis would be associated with lower survival, since hepatitis can be related to IDU,[67] who had greater unadjusted odds of death both in the current and other studies, and to liver disease,[70;71] which was a primary cause of death both in the current study and elsewhere.[86]

The better survival time in hepatitis patients in those first reporting in the ultra-active period may indicate better management of this co-morbidity is now well established, as recommended by Bonnet in 2008,[66] and there may be an effect from a reduction of recent HCV infection in patients with haemophilia reported elsewhere.[74] A 2009 Scottish study has confirmed HCV infection and IDU status are linked.[123] Interestingly, in another HIV co-morbidity, tuberculosis, mortality hazard was also lower.[176]

The AIDS deaths were mainly from AIDS defining infections. Quicker death from AIDS-related conditions post HAART could have been related to late diagnosis, which Lucas[116] states as the main remediable factor in HIV related death in the UK. The wider literature showed late diagnosis was negatively related to survival, for example among injecting drug users (Grigoryan 2009).[193] Recent studies in the UK excluding Scotland suggest late diagnosis is more probable in older adults.[109]

The reasons for any late diagnosis would need further investigation. Possibly older adults perceive risk of HIV infection to be lower. This thesis shows a steadily increasing mean age of the prevalent population living with HIV in Scotland. The aging of the HIV epidemic may also perhaps help to explain the faster progression to death from AIDS in post HAART eras found in the current study, possibly from decreased response to HAART and in some cases adherence to treatment issues (e.g. AIDS related dementia[194]). Although older HIV+ people normally have better treatment adherence than younger ones[195] specific issues such as drug interactions[25] and depression[196] may reduce adherence. Possibly stigma issues combined with lack of an acute need for care could have prevented people with AIDS defining infections reporting to services until they experienced an acute phase late in their infection. Possibly connected to the aging of the HIV pandemic, the increasing proportion of deaths from AIDS defining infection results from older people possibly being more

vulnerable than younger people to AIDS defining infections, as they are to infections generally.

The lack of any major drop in the proportion of death with AIDS post HAART, and the possible increase (when COD unknown excluded) contrasted with findings reported elsewhere in the literature, which has suggested non-AIDS deaths were an increasing proportion of deaths in HIV positive people.

11.7 Limitations

Coding

The system in place has not changed since January 1999. Prior to that it changed in April 1990 and January 1966. There can be usually up to six causes of death on the certificate. The direct cause is listed first, followed by up to three antecedent causes, the last of which is termed the 'underlying' cause, and two associated conditions. The English and Welsh system differs slightly from the Scottish in having up to two antecedent causes and three associated conditions. Some deaths may have been registered in England. These factors mean an 'any cause' analysis (taking causes from any of the six coding positions) may be the most robust for COD using this Scottish data, as less dependent on judgment for selecting primary COD.

The type of coding used (e.g. any cause or primary cause) and detailed coding rules may affect comparability between this and other studies.

Life table

A paper by the ART collaboration (2008) used abridged life tables because:

> "Large populations are needed to overcome systematic and random variations in mortality when building complete life tables"

This was despite having 43,355 cases and 2050 deaths post 1996. The ART used the abridged life tables to compare life expectancies at age of 20 in 1996–99, 2000–02, and 2003–05. Had there been sufficient time, this could have been the preferred approach for this MPH project. An abridged life table could have been constructed for the final or middle years in each era.

COD unknown

The proportion with COD unknown increased between pre-HAART era of first report and later eras. That could be related to greater follow-up time needed with the increased survival. Survival curves for COD unknown were between those for AIDS-defining and non-AIDS deaths, suggesting there was no bias to one or the other.

12. Conclusions

Annual deaths recorded on the HPS HIV database peaked in those first reporting in 1995, immediately as HAART was introduced, and age SMRs reduced consistently through the eras of first report. From pre-HAART to ultra-active HAART there was a reduction in IDU transmission (42% to 23%), an increase in sexual transmission routes (heterosexual route from 17% up to 34%, and MSM from 33% up to 36%), an increasing proportion of females (24%-32%), and a decreasing proportion of white people (95% down to 62%). Survival times have improved, but for those who died AIDS was increasingly likely to be involved, and was associated with worse survival time in each succeeding era, possibly related to late diagnosis. Life expectancy in Scotland at 23 years for a 20 year old in 2008 was at the lower end of the range found in other studies.

Odds ratios of death reduced over HAART eras and adjusted ORs showed a stronger reduction. Sex and IDU status were not associated with different risk of death after adjusting for covariates. White people had over five times greater adjusted odds for death than non white people, around half their unadjusted odds. MSM, heterosexual and IDU transmission had lower adjusted odds of death than blood tissue transfer, and these were lower than their unadjusted odds.

Those older at first report and those with lower CD4 counts at first report had higher adjusted odds of death for each unit increase in year of age or unit drop in CD4 count. In contrast unadjusted odds for age were lower for each year of increase ($p<0.001$). Unadjusted were similar to adjusted odds.

The proportion of deaths with known COD that were with an AIDS COD in any position rose from 75% for those first reporting pre-HAART to over 90% in those first reporting in ultra-active HAART. AIDS-defining infections were the primary cause of

over 80% of deaths from AIDS for those first reporting in ultra-active HAART. Survival time fell and proportional Hazard of death increased for AIDS deaths in comparison to deaths from other causes over the periods of HAART first report, in contrast to the falling hazard for death in the HIV+ population generally.

In brief, the prevalent HIV positive population in Scotland has an increasing mean age, is growing in size, mortality has dramatically decreased, survival improved, (though not as much as in some other cohorts) and transmission patterns have changed. These factors are common to most developed countries. In Scotland, those who die increasingly appear to succumb to AIDS defining infection relatively quickly after first report. This has not been found elsewhere. Although there is some Scottish evidence of increased mortality in HCV and HIV co-infection we did not find any deaths with any hepatitis in the latest ultra-active era. In addition, evidence from this study suggests that life expectancy at age 20 for people presenting with HIV in Scotland may be at the lower end of estimates reported for the developed world.

12.6 Recommendations

Recommendations: Policy

1. Protect the health of those who are HIV positive and the wider population:
    - earlier HAART without breaks, to get HAART established before patients, reach older ages at which HAART is less well tolerated, and to reduce infectivity (finding of rising age at first report)
    - ongoing support for safe injecting practices, (to maintain reduction in HIV+IDU)
    - consider options to address the issue of infection abroad, (in view of rising proportion infected abroad)
    - encourage safer sex in both heterosexuals and MSM at older ages, to limit transmission of HIV, HPV related cancers, infections (in view of rising proportion of sexual transmission).

2. Promote healthy lifestyles – this population may have aggravated risks from smoking, and alcohol (though no evidence in Scotland from mortality data)

3. Support therapy adherence, especially for some older people to reduce effects of drug interactions and cognitive deficits including depression (in view of rising mean age of prevalent population).
4. Address equalities issues (specifically for aging women living with HIV) (in view of rising proportion of women and evidence from literature).

Data issues

1. enhance methods to improve follow up data collection (a UK Database? though logistics may be problematic owing to coding differences),
2. include socio-economic deprivation information in the dataset, (feasible if linked to address?)
3. enable limited collection of morbidity data to better answer some of the unresolved questions above,
4. in data linkage, retain the distinction between English and Scottish registered deaths and direct, antecedent, underlying, and associated conditions,
5. give medical students training on methods for recording cause of death, (to supplement guidance issued in September 2009[197])
6. develop guidelines for consistent life table methods for use in HIV/AIDS studies to support comparisons.

Management issues

An economic analysis of the future cost of HAART drugs and other services for people living with an HIV positive test over their increased life expectancy is needed for evidence-based planning.[198]

Recommendations: Clinical services

It is not yet clear from mortality data if there will be a need for greater health service capacity, in addition to HIV services, or within which service types, but dementia, geriatric, screening and nursing care,[199] are possible candidates. Linked to the rising proportion of infections found, opportunistic HIV testing for people presenting to services with possible AIDS-defining infections such as candidiasis could be a useful

measure for secondary prevention provided suitable consent procedures were in place.

Recommendations: Future research

1. It is not proven whether in Scotland it would be effective to introduce additional cardiovascular and cancer risk screening for HIV positive people. This needs research.

2. Investigate possible reasons for late diagnosis., especially in older people and ways in which this can be countered effectively.

3. Further basic research to develop new forms of HAART better tolerated by older people.

4. Further survival time analysis for 'any' mention of diagnostic groups in any position

5. The SMRs did not adjust for person years spent in each age group. Lexis expansion is a further more sophisticated technique to adjust for time in the study *in each age range*, and would be a next step in the analysis, but it would have been a large exercise with this large dataset.

Cause of death

Using any cause of death (from any position of the death certificate) would be a next step in survival time analysis, and would be a first step (but resource intensive) in giving an impression of morbidity as well as mortality in this population. A further question of interest would be to assess the change in OR for death or morbidity from CV, cancer, infections, and accidents/suicide in relation to time spent on HAART.

Adjusted Odds Ratios of death

Further adjustment of the binomial regression model could be tried to find a model that could be stratified by era of HAART first report to identify each era the factors that those who died who first reported in that era were most likely to have died of.

In summary, further work is needed on the demographics and public health implications (possible excess morbidity) of the increasing mean age and population of people living with a positive HIV test in Scotland.

13. Lessons learned

The project has taught me a great deal of technical detail about the principles of multivariate analysis and practicalities of using SPSS. It has underlined for me the importance of checking key definitions used in the literature and using compatible ones to help in setting the project in context in the discussion. It has reaffirmed the value of thorough data preparation in supporting the reproducibility of analyses, which is for me the key to keeping motivated as a professional researcher, and is strongly connected to the integrity of the research and the ethics of carrying it out.

I have learned the basics of life table construction. I would recommend every MPH teaches this, since life expectancy is still so commonly used to compare population health, and is intuitively understood.

I have more fully realised the importance of focusing on the accessibility to the reader of the final product, in addition to ensuring the validity of methods.

And finally, it has re-taught me that there are no shortcuts, and that good research continues to be more challenging than you think it will be. At the same time, in interpreting results and the literature I have learned the value of serial chance encounters and how to use ideas from them in navigating and making sense of complexities. The importance of networking and sharing issues with other key parties was highlighted to me as part of that.

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Appendix 1 Search strategies

Table A1.1 Search 1

	Search terms	No. results
▫1	((HIV or Aids or 'Human Immun?deficiency' or 'Acquired Immun?deficiency') and (Survival or 'Life expectancy' or mortality or "cause of death") and (ART or 'anti?retroviral*')).tw.	6643
2	(old* or elder* or ag?ing or aged).tw.	1269625
3	1 and 2	752
4	((HIV or Aids or 'Human Immun?deficiency' or 'Acquired Immun?deficiency') and (Survival or 'Life expectancy' or mortality or "cause of death") and (ART or 'anti?retroviral*')).ti,ab.	6484
5	(old* or elder* or ag?ing or aged).ti,ab.	1252420
6	4 and 5	681
7	((HIV or Aids or 'Human Immun?deficiency' or 'Acquired Immun?deficiency') and (Survival or 'Life expectancy' or mortality or "cause of death") and (ART or 'anti?retroviral*')).ti.	421
8	(old* or elder* or ag?ing or aged).ti.	243136
9	7 and 8	4
10	remove duplicates from 3	495
11	limit 10 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	450
12	limit 11 to human [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	442
13	remove duplicates from 6	424
14	limit 13 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	379
15	limit 14 to human [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	371
16	remove duplicates from 9	2
17	limit 16 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	2
18	limit 17 to human [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	2 **VIEW 1**
19	15 not 18	369 **VIEW 2**
20	12 not (15 or 18)	71
21	(CVD or cardio?vascular or stroke or heart attack* or agina or arteriosclerosis or tumo?r* or neoplasm* or cancer*).tw.	1975102
22	1 and 21	829
23	remove duplicates from 22	516
24	limit 23 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	427
25	limit 24 to human [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	422
26	(CVD or cardio?vascular or stroke or heart attack* or agina or arteriosclerosis or tumo?r* or neoplasm* or cancer*).ti,ab.	1967950
27	4 and 26	791
28	remove duplicates from 27	478
29	limit 28 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	389
30	limit 29 to human [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	385
31	(CVD or cardio?vascular or stroke or heart attack* or agina or arteriosclerosis or tumo?r* or neoplasm* or cancer*).ti.	907772
32	7 and 31	3
33	remove duplicates from 32	2
34	limit 33 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	2
35	limit 34 to human [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR,HMIC; records were retained]	2
36	30 not 35	383
37	25 not (30 or 35)	37
38	30 or 36 or 37	422
39	38 not 3	366

40	Developing countries/	41882
41	exp africa/ or exp asia/ or exp atlantic islands/ or exp historical geographic locations/ or exp indian ocean islands/ or exp oceania/ or exp "oceans and seas"/ or exp pacific islands/	670302
42	(africa* or asia or india or pakistan or oceania or pacific island* or developing countr* or third world).tw.	217503
43	40 or 41 or 42	797714
44	39 not 43	319
45	remove duplicates from 44	319 **VIEW 3**

VIEW 1 3 concepts*: search of title or abstract minus duplicates and limited
VIEW 2 3 concepts search of title or abstract minus title
VIEW 3 3 concepts text word/title and abstract +CVD or cancer
*3 concepts: HIV/AIDS, survival, LE, mortality or COD and ART

Table A1.2 Search 2

	Search terms	**No. results**
1	((HIV or Aids or 'Human Immun?deficiency' or 'Acquired Immun?deficiency') and (Survival or 'Life expectancy' or mortality or "cause of death") and (ART or 'anti?retroviral*)).tw.	**3110**
2	(old* or elder* or ag?ing or aged).tw.	**611333**
3	1 and 2	**341**
4	HIV Core Protein p24/ or HIV Long-Term Survivors/ or exp HIV Infections/ or HIV Enhancer/ or exp HIV/ or HIV Antibodies/ or HIV Seroprevalence/ or exp HIV Antigens/	**129619**
5	exp anti-retroviral agents/ or anti-hiv agents/	**38222**
6	life expectancy/ or life tables/ or exp morbidity/ or mortality/ or "cause of death"/ or fatal outcome/ or hospital mortality/ or maternal mortality/ or survival rate/	**332970**
7	exp Survival Analysis/ or Survival/	**92427**
8	disease-free survival/	**24515**
9	6 or 7 or 8	**405385**
10	4 and 5 and 9	**1764**
11	aged/ or middle aged/	**1512727**
12	exp Aging/	**75956**
13	11 or 12	**1557576**
14	10 and 13	**547**
15	14 not 3	**523**
16	limit 15 to (english language and humans)	**497**
17	Developing Countries/	**24118**
18	exp africa/ or exp asia/ or exp atlantic islands/ or exp historical geographic locations/ or exp indian ocean islands/ or exp oceania/ or exp "oceans and seas"/ or exp pacific islands/	**409061**
19	(africa* or asia or india or pakistan or oceania or pacific island* or developing countr* or third world).tw.	**109420**
20	17 or 18 or 19	**472168**
21	16 not 20 (view 1 (3 concepts: HIV and survival and cause of death and ART) and aging, minus developing countries, and minus textword results)	**394 VIEW 1**
22	exp neoplasms/ or exp cardiovascular diseases/	**1569632**
23	10 and 22	**191**
24	23 not 3	**187**
25	24 not 20	**173**
26	limit 25 to (english language and humans)	**157**
27	**26 not 21 (view 2 3 concepts and CVD or cancer minus text word results and limited (not specific to age)**	**82 VIEW 2**

VIEW 1 3 concepts* search of text word + aging
VIEW 2 3 concepts + search of text words CVD or cancer
*3 concepts: HIV/AIDS, survival, LE, mortality or COD and ART

Table A1.3 Search 3

	Search terms	**No. results**
1	((HIV or Aids or 'Human Immun?deficiency' or 'Acquired Immun?deficiency') and (Survival or 'Life expectancy' or mortality or "cause of death") and (ART or 'anti?retroviral*)).tw.	**3171**
2	(old* or elder* or ag?ing or aged).tw.	**580141**
3	1 and 2	**319**
4	Developing Countries/	**16515**
5	exp africa/ or exp asia/ or exp atlantic islands/ or exp historical geographic locations/ or exp indian ocean islands/ or exp oceania/ or exp "oceans and seas"/ or exp pacific islands/	**243032**
6	(africa* or asia or india or pakistan or oceania or pacific island* or developing countr* or third world).tw.	**98842**
7	4 or 5 or 6	**300059**
8	exp human immunodeficiency virus/ or exp human immunodeficiency virus infection/	**131837**
9	exp acquired immune deficiency syndrome/	**37478**
10	8 or 9	**131837**
11	antiretrovirus agent/	**23449**
12	exp survival/	**214683**
13	mortality/ or cancer mortality/	**178658**
14	morbidity/	**81361**
15	"cause of death"/	**30216**
16	12 or 13 or 14 or 15	**411442**
17	aging/ or postmaturity/	**63632**
18	aged/	**788715**
19	17 or 18	**825856**
20	exp cardiovascular disease/	**942732**
21	exp neoplasm/	**997228**
22	20 or 21	**1833514**
23	10 and 11 and 16 and 19	**249**
24	23 not 3	**215**
25	10 and 11 and 16 and 22	**981**
26	25 not (3 or 23)	**858**
27	developing country/	**16515**
28	exp Africa/	**52785**
29	exp Asia/	**166978**
30	exp "South and Central America"/	**33102**
31	27 or 28 or 29 or 30	**255525**
32	24 not 31	**170**
33	limit 32 to (human and english language)	**165 VIEW 1**
34	26 not 31	**757**
35	**limit 34 to (human and english language)**	**671 VIEW 2**

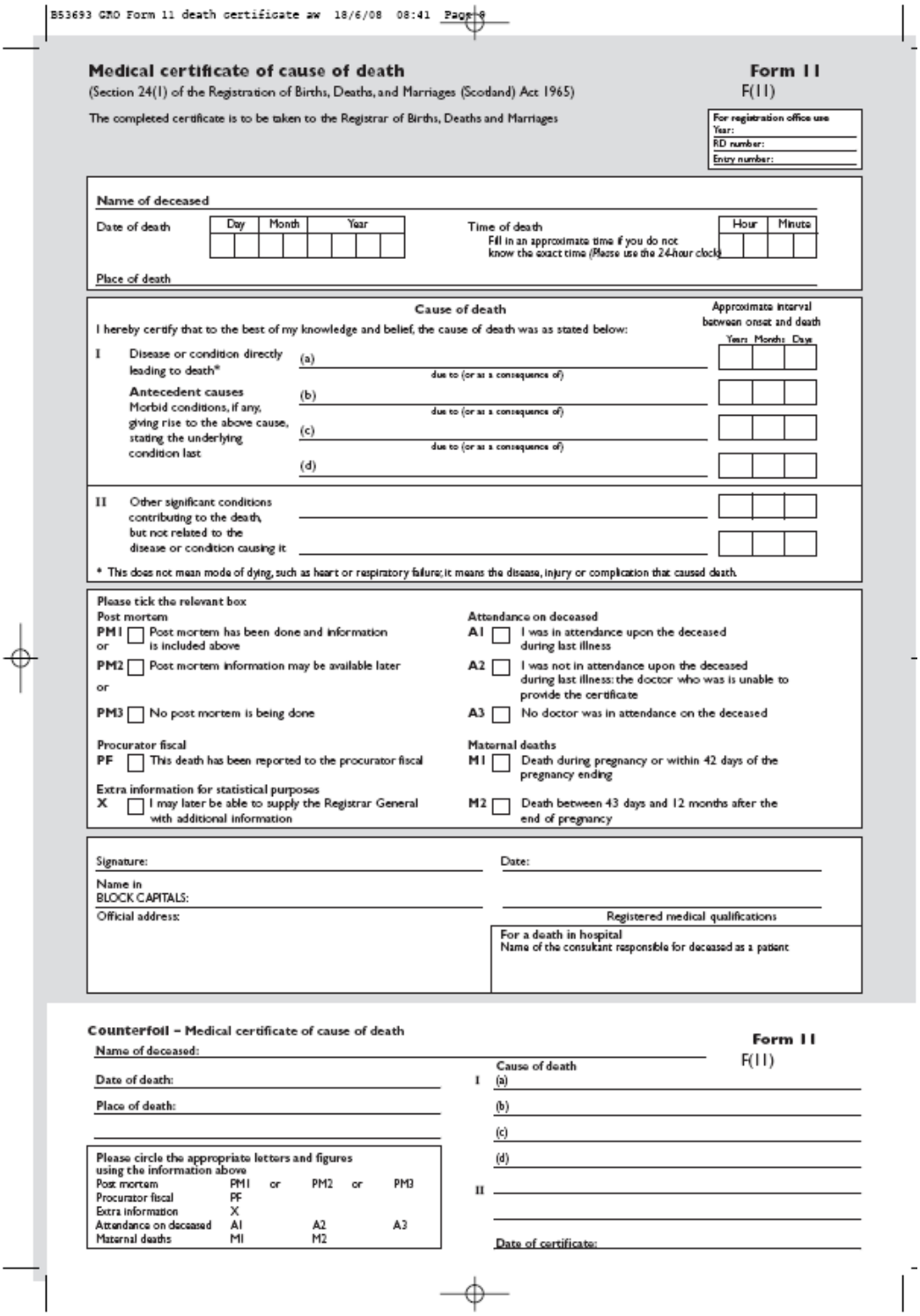
VIEW 1 3 concepts* + aging minus text word results
VIEW 2 3 concepts + CVD or cancer minus text word results and dev countries
*3 concepts: HIV/AIDS, survival, LE, mortality or COD and ART and dev countries

Papers were excluded if they were duplicates, or on reading the abstract (if available) or title (if not) or they were broadly within the following categories, with the overriding proviso that papers were retained if judged relevant to the likely future burden on health and social care services from increasing survival among HIV+ people, especially in relation to aging with HIV:

Table A1.4 Exclusion criteria

1. Not specifically about survival or mortality (or not about relevant survival – e.g. information from a clinical trial rather than epidemiologically valid information relevant to population survival),
2. children or adolescents,
3. conditions in the developing world,
4. treatment - including treatment descriptions, tests, treatment comparisons, clinical descriptions, guidelines, diagnosis and management,
5. economics of drugs,
6. rare specific conditions (e.g. liver, kidney and others),
7. not a large study and the sample was treatment or service based,
8. specific condition in a specific service based setting unless large study or a common condition,
9. cell research about mechanisms of HIV infection,
10. psychological health and wellbeing (unless relevant to older people's medication compliance),
11. ICU survival,
12. incidence/prevalence of morbidities unless relevant for the service burden in older people,
13. progression and prognosis of disease if not survival,
14. treatment resistance,
15. treatment adherence (unless relevant to older people),
16. drug safety.

Appendix 2 Medical certificate of cause of death in use in Scotland (2010)[h]



B53693 GRO Form 11 death certificate aw 18/6/08 08:41 Page 1

Medical certificate of cause of death — **Form 11** F(11)

(Section 24(1) of the Registration of Births, Deaths, and Marriages (Scotland) Act 1965)

The completed certificate is to be taken to the Registrar of Births, Deaths and Marriages

For registration office use
Year:
RD number:
Entry number:

Name of deceased

Date of death — Day | Month | Year

Time of death — Hour | Minute
Fill in an approximate time if you do not know the exact time (Please use the 24-hour clock)

Place of death

Cause of death

I hereby certify that to the best of my knowledge and belief, the cause of death was as stated below:

Approximate interval between onset and death — Years | Months | Days

I Disease or condition directly leading to death* (a)

due to (or as a consequence of)

Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last

(b)

due to (or as a consequence of)

(c)

due to (or as a consequence of)

(d)

II Other significant conditions contributing to the death, but not related to the disease or condition causing it

* This does not mean mode of dying, such as heart or respiratory failure; it means the disease, injury or complication that caused death.

Please tick the relevant box

Post mortem

PM1 ☐ Post mortem has been done and information is included above

or

PM2 ☐ Post mortem information may be available later

or

PM3 ☐ No post mortem is being done

Attendance on deceased

A1 ☐ I was in attendance upon the deceased during last illness

A2 ☐ I was not in attendance upon the deceased during last illness: the doctor who was is unable to provide the certificate

A3 ☐ No doctor was in attendance on the deceased

Procurator fiscal

PF ☐ This death has been reported to the procurator fiscal

Maternal deaths

M1 ☐ Death during pregnancy or within 42 days of the pregnancy ending

M2 ☐ Death between 43 days and 12 months after the end of pregnancy

Extra information for statistical purposes

X ☐ I may later be able to supply the Registrar General with additional information

Signature: Date:

Name in BLOCK CAPITALS:

Registered medical qualifications

Official address:

For a death in hospital
Name of the consultant responsible for deceased as a patient

Counterfoil – Medical certificate of cause of death — **Form 11** F(11)

Name of deceased:

Date of death:

Place of death:

Cause of death

I (a)

(b)

(c)

(d)

II

Date of certificate:

Please circle the appropriate letters and figures using the information above

Post mortem	PM1	or	PM2	or	PM3
Procurator fiscal	PF				
Extra information	X				
Attendance on deceased	A1		A2		A3
Maternal deaths	M1		M2		

[h] http://www.sehd.scot.nhs.uk/cmo/CMO(2009)10.pdf

Appendix 3 Diagnostic groups

1 Infections
2 HIV
3 Hep C
4 AIDs defining infection
4 HIV_AIDs defining infection
5 Cancer excl AIDs defining cancer
6 AIDs defining cancer
6 HIV AIDS defining cancer
7 Diabetes Mellitus
8 Adrenal gland disorder
9 Nutritional and Metabolic disorders
10 Immune and Blood disorders
10 Immune and blood disorders (resulting from HIV)
10 HIV and AIDS defining immune and blood disorder
11 Musculo-skeletal and connective tissue
12 Symptoms and signs NEC
13 Mental health
14 Alcohol-related
15 Drug related
16 Neurological and eye
16 AIDS defining Neurological and eye
16 HIV AIDS defining Neurological and eye
17 CV system
18 CV Thrombosis
19 CV Haemorrhage
19 AIDs defining respiratory
20 Other respiratory (not AIDs defining)
21 Digestive/Gastro-intestinal
22 Hepato-biliary
23 Pancreatitis (not used, coded under digestive/GI)
24 Renal/Genito-urinary
25 Skin
26 Rheumatoid arthritis (not used, under 11 musc-skeletal)
27 Bone infection (not used, under 11 musc-skeletal)
28 AIDs defining other
28 HIV AIDS defining other
28 Other
29 Unknown cause
30 Other trauma (inc accidents, acc. poisoning)
31 Suicide, poss. Suicide/self harm
32 No such code
33 HepB or Hep unspecified

Appendix 4 HPS Datafields

(Note there was additional separate data on cause of death)

HPSHIVRefNo - ID number
Sex
DOB
HBCaseAllocated - health board
Dead
DOD - date of death
HPSHIVReportDate - Date first reported as case to HPS
NewDx_KnownCase beware of new diagnosis here it likely means first diagnosis in this country.
Transmission - transmission category
HeteoTransSubCat - more specifics if heterosexual e.g. sex with someone from high risk group
InfectedExScotland - if infected outside scotland
Ethnicity
AIDSDxDate - date given an AIDS disgnosis
EarliestAttendance - first attendance at treatment and care unit
EarliestCD4Count
EarliestVLLabDate - viral load count
EarliestVLGroup - Viral load group
TotalAttendances
HighestARTStatus - highest level of treatment given (triple, double, single)
LatestAttendance - at clinic
LatestCD4Count
LatestCD4Group - <200, 200-350 and >350
LatestVLLabDate
LatestVLGroup
LatestARTStatus - latest treatment

Appendix 5 Ethics approval

University of Glasgow Faculty of Medicine

Dr Andrew Millard
Scottish Public Health Network
C/o NHS Health Scotland
4th Floor
Elphinstone House
65 West Regent Street
Glasgow
G2 2AF

11.01.10

Dear Dr Millard

Medical Faculty Ethics Committee
Project Title: Modelling the impact of aging in people living with HIV in Scotland

Project No.: FM01509

The Faculty Ethics Committee has reviewed your application and has agreed that there is no objection on ethical grounds to the proposed study. They are happy therefore to approve the project, subject to the following conditions:

- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- If the study does not start within three years of the date of this letter, the project should be resubmitted.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Dr Una MacLeod
Faculty Ethics Officer

Dr U MacLeod
Clinical Senior Lecturer

General Practice & Primary Care, Division of Community Based Sciences, University of Glasgow, 1 Horselethill Road, Glasgow, G12 9LX

Tel: 0141 330 8328
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University of Glasgow | Faculty of Medicine

Dr Andrew Millard
Scottish Public Health Network
C/o NHS Health Scotland
4th Floor
Elphinstone House
65 West Regent Street
Glasgow G2 2AF

(June 2010)

Dear Dr Millard

Medical Faculty Ethics Committee
Project Title: Modelling the impact of aging in people living with HIV in Scotland

Project No.: FM01509

The Faculty Ethics Committee has reviewed your request to revise question 11 of your Ethics Application Form from "there are no children in the database" to "there are children in the database and they are subject to the same confidentiality requirements as other subjects. They are included to give a complete picture of mortality, survival and life expectancy in this disease." I would like to confirm that there are no ethical objections to the proposed change. I am therefore happy to approve the amended project subject to the following conditions:

- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- If the study does not start within three years of the date of this letter, the project should be resubmitted.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Dr Una MacLeod
Faculty Ethics Officer

Dr U MacLeod
Clinical Senior Lecturer

General Practice & Primary Care, Division of Community Based Sciences, University of Glasgow, 1 Horselethill Road, Glasgow, G12 9LX
Tel: 0141 330 8328
E-mail: u.macleod@clinmed.gla.ac.uk

Appendix 6 COD groups

Full list of cause of death groups by primary COD, and whether AIDS defining.

Non AIDS defining Primary Cause of Death (sorted by Pre-HAART frequency)	Total
Suicide, poss. Suicide/self harm	46
Other trauma (inc accidents, accidental poisoning)	47
CV system	48
Hepato-biliary	43
Infections	38
Other respiratory (not AIDS defining)	35
Cancer excl AIDS defining cancer	33
Drug related	20
Digestive/Gastro-intestinal	14
Hep C	14
Hep B or Hep unspecified	12
Immune and Blood disorders	14
CV Thrombosis	11
CV Haemorrhage	10
*Neurological and eye	*
*Renal/Genito-urinary	*
*Mental health	*
Alcohol-related	*
*Nutritional and Metabolic disorders	*
*Unknown cause	*
*Musculo-skeletal and connective tissue	*
*Adrenal gland disorder	*
Total	426

*Other non AIDS

AIDS defining Primary Cause of Death (sorted by Pre-HAART frequency)	Total
AIDS defining respiratory	281
AIDS defining infection	303
HIV (only)	68
AIDS defining cancer	71
AIDS defining Neurological and eye	31
AIDS defining other	11
Total	765

	Pre HAART (%)	Early HAART (%)	Late HAART (%)	Ultra-active HAART (%)	Total
COD unknown (primary cause or any cause)**	323 (22.79)	34 (47.89)	25 (43.10)	20 (42.55)	402 (25.24)

**note p<0.000 for chi-square for trend over 4 eras, not over post HAART eras (<0.546)

Appendix 7 Further Life tables

Table A7.1 Current complete Life Table for life expectancy from birth for first reports from 1981-2009 who had not died by 2008 or died in 2008

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
0	4235	0	4235.000	0	.00	1.00	1.00	.00	4235	179765.5	42.448
1	4235	0	4235.000	0	.00	1.00	1.00	.00	4235	175530.5	41.448
2	4235	1	4234.500	0	.00	1.00	1.00	.00	4235	171295.5	40.452
3	4234	2	4233.000	1	.00	1.00	1.00	.00	4233.5	167060.5	39.466
4	4231	2	4230.000	0	.00	1.00	1.00	.00	4231	162827	38.493
5	4229	2	4228.000	0	.00	1.00	1.00	.00	4229	158596	37.511
6	4227	3	4225.500	0	.00	1.00	1.00	.00	4227	154367	36.532
7	4224	4	4222.000	0	.00	1.00	1.00	.00	4224	150140	35.561
8	4220	5	4217.500	0	.00	1.00	1.00	.00	4220	145916	34.598
9	4215	2	4214.000	0	.00	1.00	1.00	.00	4215	141696	33.625
10	4213	3	4211.500	0	.00	1.00	1.00	.00	4213	137481	32.644
11	4210	3	4208.500	0	.00	1.00	1.00	.00	4210	133268	31.666
12	4207	3	4205.500	0	.00	1.00	1.00	.00	4207	129058	30.688
13	4204	5	4201.500	0	.00	1.00	1.00	.00	4204	124851	29.716
14	4199	2	4198.000	0	.00	1.00	1.00	.00	4199	120647	28.739
15	4197	7	4193.500	0	.00	1.00	1.00	.00	4197	116448	27.769
16	4190	1	4189.500	0	.00	1.00	1.00	.00	4190	112251	26.793

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
17	4189	4	4187.000	0	.00	1.00	1.00	.00	4189	108061	25.809
18	4185	3	4183.500	0	.00	1.00	1.00	.00	4185	103872	24.829
19	4182	4	4180.000	0	.00	1.00	1.00	.00	4182	99687	23.849
20	4178	9	4173.500	0	.00	1.00	1.00	.00	4178	95505	22.884
21	4169	13	4162.500	0	.00	1.00	1.00	.00	4169	91327	21.940
22	4156	14	4149.000	0	.00	1.00	1.00	.00	4156	87158	21.007
23	4142	27	4128.500	0	.00	1.00	1.00	.00	4142	83002	20.105
24	4115	29	4100.500	0	.00	1.00	1.00	.00	4115	78860	19.232
25	4086	55	4058.500	0	.00	1.00	1.00	.00	4086	74745	18.417
26	4031	71	3995.500	0	.00	1.00	1.00	.00	4031	70659	17.685
27	3960	57	3931.500	0	.00	1.00	1.00	.00	3960	66628	16.947
28	3903	74	3866.000	2	.00	1.00	1.00	.00	3902	62668	16.210
29	3827	91	3781.500	0	.00	1.00	1.00	.00	3827	58766	15.540
30	3736	92	3690.000	0	.00	1.00	1.00	.00	3736	54939	14.889
31	3644	74	3607.000	1	.00	1.00	1.00	.00	3643.5	51203	14.195
32	3569	83	3527.500	0	.00	1.00	1.00	.00	3569	47559.5	13.482
33	3486	139	3416.500	0	.00	1.00	1.00	.00	3486	43990.5	12.876
34	3347	128	3283.000	2	.00	1.00	1.00	.00	3346	40504.5	12.338
35	3217	109	3162.500	1	.00	1.00	1.00	.00	3216.5	37158.5	11.750
36	3107	131	3041.500	0	.00	1.00	1.00	.00	3107	33942	11.160
37	2976	132	2910.000	0	.00	1.00	1.00	.00	2976	30835	10.596
38	2844	197	2745.500	0	.00	1.00	1.00	.00	2844	27859	10.147
39	2647	151	2571.500	0	.00	1.00	1.00	.00	2647	25015	9.728

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
40	2496	195	2398.500	2	.00	1.00	1.00	.00	2495	22368	9.326
41	2299	154	2222.000	1	.00	1.00	1.00	.00	2298.5	19873	8.944
42	2144	196	2046.000	0	.00	1.00	1.00	.00	2144	17574.5	8.590
43	1948	193	1851.500	1	.00	1.00	1.00	.00	1947.5	15430.5	8.334
44	1754	189	1659.500	2	.00	1.00	1.00	.00	1753	13483	8.125
45	1563	152	1487.000	4	.00	1.00	.99	.00	1561	11730	7.888
46	1407	169	1322.500	2	.00	1.00	.99	.00	1406	10169	7.689
47	1236	157	1157.500	1	.00	1.00	.99	.00	1235.5	8763	7.571
48	1078	149	1003.500	1	.00	1.00	.99	.00	1077.5	7527.5	7.501
49	928	127	864.500	0	.00	1.00	.99	.00	928	6450	7.461
50	801	87	757.500	1	.00	1.00	.99	.00	800.5	5522	7.290
51	713	92	667.000	3	.00	1.00	.98	.00	711.5	4721.5	7.079
52	618	80	578.000	1	.00	1.00	.98	.00	617.5	4010	6.938
53	537	75	499.500	1	.00	1.00	.98	.00	536.5	3392.5	6.792
54	461	81	420.500	1	.00	1.00	.98	.01	460.5	2856	6.792
55	379	51	353.500	0	.00	1.00	.98	.01	379	2395.5	6.777
56	328	43	306.500	0	.00	1.00	.98	.01	328	2016.5	6.579
57	285	44	263.000	0	.00	1.00	.98	.01	285	1688.5	6.420
58	241	46	218.000	2	.01	.99	.97	.01	240	1403.5	6.438
59	193	21	182.500	1	.01	.99	.96	.01	192.5	1163.5	6.375
60	171	26	158.000	0	.00	1.00	.96	.01	171	971	6.146
61	145	28	131.000	0	.00	1.00	.96	.01	145	800	6.107
62	117	17	108.500	0	.00	1.00	.96	.01	117	655	6.037

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
63	100	11	94.500	0	.00	1.00	.96	.01	100	538	5.693
64	89	13	82.500	0	.00	1.00	.96	.01	89	438	5.309
65	76	14	69.000	0	.00	1.00	.96	.01	76	349	5.058
66	62	15	54.500	0	.00	1.00	.96	.01	62	273	5.009
67	47	14	40.000	0	.00	1.00	.96	.01	47	211	5.275
68	33	5	30.500	0	.00	1.00	.96	.01	33	164	5.377
69	28	4	26.000	0	.00	1.00	.96	.01	28	131	5.038
70	24	8	20.000	0	.00	1.00	.96	.01	24	103	5.150
71	16	2	15.000	0	.00	1.00	.96	.01	16	79	5.267
72	14	2	13.000	0	.00	1.00	.96	.01	14	63	4.846
73	12	3	10.500	0	.00	1.00	.96	.01	12	49	4.667
74	9	1	8.500	0	.00	1.00	.96	.01	9	37	4.353
75	8	4	6.000	0	.00	1.00	.96	.01	8	28	4.667
76	4	1	3.500	0	.00	1.00	.96	.01	4	20	5.714
77	3	0	3.000	0	.00	1.00	.96	.01	3	16	5.333
78	3	0	3.000	0	.00	1.00	.96	.01	3	13	4.333
79	3	1	2.500	0	.00	1.00	.96	.01	3	10	4.000
80	2	0	2.000	0	.00	1.00	.96	.01	2	7	3.500
81	2	0	2.000	0	.00	1.00	.96	.01	2	5	2.500
82	2	1	1.500	0	.00	1.00	.96	.01	2	3	2.000
83	1	1	.500	0	.00	1.00	.96	.01	1	1	2.000

Life expectancies by year of current age and stratified by age at first report

Life Table for life expectancy from birth for first reports from 1981-2009 who had not died by 2008 or died in 2008 stratified by age at first report
Aged 0-19 at first report

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs)	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
0	228	0	228.000	0	.00	1.00	1.00	.00	228	6656.5	29.20
1	228	0	228.000	0	.00	1.00	1.00	.00	228	6428.5	28.20
2	228	1	227.500	0	.00	1.00	1.00	.00	228	6200.5	27.25
3	227	2	226.000	1	.00	1.00	1.00	.00	226.5	5972.5	26.43
4	224	2	223.000	0	.00	1.00	1.00	.00	224	5746	25.77
5	222	2	221.000	0	.00	1.00	1.00	.00	222	5522	24.99
6	220	3	218.500	0	.00	1.00	1.00	.00	220	5300	24.26
7	217	4	215.000	0	.00	1.00	1.00	.00	217	5080	23.63
8	213	5	210.500	0	.00	1.00	1.00	.00	213	4863	23.10
9	208	2	207.000	0	.00	1.00	1.00	.00	208	4650	22.46
10	206	3	204.500	0	.00	1.00	1.00	.00	206	4442	21.72
11	203	3	201.500	0	.00	1.00	1.00	.00	203	4236	21.02
12	200	3	198.500	0	.00	1.00	1.00	.00	200	4033	20.32
13	197	5	194.500	0	.00	1.00	1.00	.00	197	3833	19.71
14	192	2	191.000	0	.00	1.00	1.00	.00	192	3636	19.04
15	190	7	186.500	0	.00	1.00	1.00	.00	190	3444	18.47
16	183	1	182.500	0	.00	1.00	1.00	.00	183	3254	17.83
17	182	4	180.000	0	.00	1.00	1.00	.00	182	3071	17.06
18	178	3	176.500	0	.00	1.00	1.00	.00	178	2889	16.37
19	175	4	173.000	0	.00	1.00	1.00	.00	175	2711	15.67
20	171	6	168.000	0	.00	1.00	1.00	.00	171	2536	15.10
21	165	8	161.000	0	.00	1.00	1.00	.00	165	2365	14.69
22	157	8	153.000	0	.00	1.00	1.00	.00	157	2200	14.38

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs)	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
23	149	9	144.500	0	.00	1.00	1.00	.00	149	2043	14.14
24	140	6	137.000	0	.00	1.00	1.00	.00	140	1894	13.82
25	134	3	132.500	0	.00	1.00	1.00	.00	134	1754	13.24
26	131	5	128.500	0	.00	1.00	1.00	.00	131	1620	12.61
27	126	4	124.000	0	.00	1.00	1.00	.00	126	1489	12.01
28	122	4	120.000	0	.00	1.00	1.00	.00	122	1363	11.36
29	118	4	116.000	0	.00	1.00	1.00	.00	118	1241	10.70
30	114	3	112.500	0	.00	1.00	1.00	.00	114	1123	9.98
31	111	4	109.000	0	.00	1.00	1.00	.00	111	1009	9.26
32	107	2	106.000	0	.00	1.00	1.00	.00	107	898	8.47
33	105	7	101.500	0	.00	1.00	1.00	.00	105	791	7.79
34	98	9	93.500	0	.00	1.00	1.00	.00	98	686	7.34
35	89	6	86.000	0	.00	1.00	1.00	.00	89	588	6.84
36	83	0	83.000	0	.00	1.00	1.00	.00	83	499	6.01
37	83	4	81.000	0	.00	1.00	1.00	.00	83	416	5.14
38	79	10	74.000	0	.00	1.00	1.00	.00	79	333	4.50
39	69	7	65.500	0	.00	1.00	1.00	.00	69	254	3.88
40	62	8	58.000	0	.00	1.00	1.00	.00	62	185	3.19
41	54	15	46.500	0	.00	1.00	1.00	.00	54	123	2.65
42	39	17	30.500	0	.00	1.00	1.00	.00	39	69	2.26
43	22	16	14.000	0	.00	1.00	1.00	.00	22	30	2.14
44	6	4	4.000	0	.00	1.00	1.00	.00	6	8	2.00
45	2	2	1.000	0	.00	1.00	1.00	.00	2	2	2.00

Life Table for life expectancy from birth for first reports from 1981-2009 who had not died by 2008 or died in 2008 stratified by age at first report

Aged 20-24 at first report

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
20	604	3	602.500	0	.00	1.00	1.00	.00	604	9541	15.84
21	601	5	598.500	0	.00	1.00	1.00	.00	601	8937	14.93
22	596	6	593.000	0	.00	1.00	1.00	.00	596	8336	14.06
23	590	18	581.000	0	.00	1.00	1.00	.00	590	7740	13.32
24	572	23	560.500	0	.00	1.00	1.00	.00	572	7150	12.76
25	549	46	526.000	0	.00	1.00	1.00	.00	549	6578	12.51
26	503	48	479.000	0	.00	1.00	1.00	.00	503	6029	12.59
27	455	25	442.500	0	.00	1.00	1.00	.00	455	5526	12.49
28	430	29	415.500	0	.00	1.00	1.00	.00	430	5071	12.20
29	401	27	387.500	0	.00	1.00	1.00	.00	401	4641	11.98
30	374	16	366.000	0	.00	1.00	1.00	.00	374	4240	11.58
31	358	14	351.000	0	.00	1.00	1.00	.00	358	3866	11.01
32	344	16	336.000	0	.00	1.00	1.00	.00	344	3508	10.44
33	328	16	320.000	0	.00	1.00	1.00	.00	328	3164	9.89
34	312	11	306.500	1	.00	1.00	1.00	.00	311.5	2836	9.25
35	300	15	292.500	0	.00	1.00	1.00	.00	300	2524.5	8.63
36	285	11	279.500	0	.00	1.00	1.00	.00	285	2224.5	7.96
37	274	14	267.000	0	.00	1.00	1.00	.00	274	1939.5	7.26
38	260	19	250.500	0	.00	1.00	1.00	.00	260	1665.5	6.65
39	241	14	234.000	0	.00	1.00	1.00	.00	241	1405.5	6.01
40	227	18	218.000	1	.00	1.00	.99	.01	226.5	1164.5	5.34
41	208	16	200.000	0	.00	1.00	.99	.01	208	938	4.69
42	192	27	178.500	0	.00	1.00	.99	.01	192	730	4.09

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
43	165	22	154.000	0	.00	1.00	.99	.01	165	538	3.49
44	143	38	124.000	0	.00	1.00	.99	.01	143	373	3.01
45	105	35	87.500	2	.02	.98	.97	.02	104	230	2.63
46	68	32	52.000	0	.00	1.00	.97	.02	68	126	2.42
47	36	21	25.500	0	.00	1.00	.97	.02	36	58	2.27
48	15	9	10.500	0	.00	1.00	.97	.02	15	22	2.10
49	6	5	3.500	0	.00	1.00	.97	.02	6	7	2.00
50	1	1	.500	0	.00	1.00	.97	.02	1	1	2.00

Life Table for life expectancy from birth for first reports from 1981-2009 who had not died by 2008 or died in 2008 stratified by age at first report

Aged 25-34 at first report

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
25	1777	6	1774.000	0	.00	1.00	1.00	.00	1777	26141	14.74
26	1771	18	1762.000	0	.00	1.00	1.00	.00	1771	24364	13.83
27	1753	28	1739.000	0	.00	1.00	1.00	.00	1753	22593	12.99
28	1725	41	1704.500	2	.00	1.00	1.00	.00	1724	20840	12.23
29	1682	60	1652.000	0	.00	1.00	1.00	.00	1682	19116	11.57
30	1622	73	1585.500	0	.00	1.00	1.00	.00	1622	17434	11.00
31	1549	56	1521.000	1	.00	1.00	1.00	.00	1548.5	15812	10.40
32	1492	65	1459.500	0	.00	1.00	1.00	.00	1492	14263.5	9.77
33	1427	116	1369.000	0	.00	1.00	1.00	.00	1427	12771.5	9.33
34	1311	108	1257.000	1	.00	1.00	1.00	.00	1310.5	11344.5	9.03
35	1202	84	1160.000	1	.00	1.00	1.00	.00	1201.5	10034	8.65
36	1117	105	1064.500	0	.00	1.00	1.00	.00	1117	8832.5	8.30
37	1012	79	972.500	0	.00	1.00	1.00	.00	1012	7715.5	7.93
38	933	106	880.000	0	.00	1.00	1.00	.00	933	6703.5	7.62
39	827	80	787.000	0	.00	1.00	1.00	.00	827	5770.5	7.33
40	747	79	707.500	1	.00	1.00	1.00	.00	746.5	4943.5	6.99
41	667	66	634.000	1	.00	1.00	.99	.00	666.5	4197	6.62
42	600	67	566.500	0	.00	1.00	.99	.00	600	3530.5	6.23
43	533	62	502.000	1	.00	1.00	.99	.00	532.5	2930.5	5.84
44	470	60	440.000	1	.00	1.00	.99	.00	469.5	2398	5.45
45	409	51	383.500	2	.01	.99	.98	.01	408	1928.5	5.03
46	356	55	328.500	0	.00	1.00	.98	.01	356	1520.5	4.63
47	301	62	270.000	0	.00	1.00	.98	.01	301	1164.5	4.31
48	239	58	210.000	0	.00	1.00	.98	.01	239	863.5	4.11

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
49	181	45	158.500	0	.00	1.00	.98	.01	181	624.5	3.94
50	136	36	118.000	0	.00	1.00	.98	.01	136	443.5	3.76
51	100	28	86.000	1	.01	.99	.97	.01	99.5	307.5	3.58
52	71	17	62.500	0	.00	1.00	.97	.01	71	208	3.33
53	54	16	46.000	0	.00	1.00	.97	.01	54	137	2.98
54	38	17	29.500	0	.00	1.00	.97	.01	38	83	2.81
55	21	8	17.000	0	.00	1.00	.97	.01	21	45	2.65
56	13	5	10.500	0	.00	1.00	.97	.01	13	24	2.29
57	8	5	5.500	0	.00	1.00	.97	.01	8	11	2.00
58	3	3	1.500	0	.00	1.00	.97	.01	3	3	2.00

Life Table for life expectancy from birth for first reports from 1981-2009 who had not died by 2008 or died in 2008 stratified by age at first report

Aged 35-44 at first report

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
35	1129	4	1127.000	0	.00	1.00	1.00	.00	1129	12835.5	11.39
36	1125	15	1117.500	0	.00	1.00	1.00	.00	1125	11706.5	10.48
37	1110	35	1092.500	0	.00	1.00	1.00	.00	1110	10581.5	9.69
38	1075	62	1044.000	0	.00	1.00	1.00	.00	1075	9471.5	9.07
39	1013	50	988.000	0	.00	1.00	1.00	.00	1013	8396.5	8.50
40	963	90	918.000	0	.00	1.00	1.00	.00	963	7383.5	8.04
41	873	57	844.500	0	.00	1.00	1.00	.00	873	6420.5	7.60
42	816	85	773.500	0	.00	1.00	1.00	.00	816	5547.5	7.17
43	731	93	684.500	0	.00	1.00	1.00	.00	731	4731.5	6.91
44	638	87	594.500	1	.00	1.00	1.00	.00	637.5	4000.5	6.73
45	550	59	520.500	0	.00	1.00	1.00	.00	550	3363	6.46
46	491	79	451.500	1	.00	1.00	1.00	.00	490.5	2813	6.23
47	411	59	381.500	0	.00	1.00	1.00	.00	411	2322.5	6.09
48	352	53	325.500	1	.00	1.00	.99	.00	351.5	1911.5	5.87
49	298	48	274.000	0	.00	1.00	.99	.00	298	1560	5.69
50	250	34	233.000	0	.00	1.00	.99	.00	250	1262	5.42
51	216	33	199.500	2	.01	.99	.98	.01	215	1012	5.07
52	181	35	163.500	1	.01	.99	.98	.01	180.5	797	4.87
53	145	22	134.000	1	.01	.99	.97	.01	144.5	616.5	4.60
54	122	27	108.500	1	.01	.99	.96	.02	121.5	472	4.35
55	94	22	83.000	0	.00	1.00	.96	.02	94	350.5	4.22
56	72	12	66.000	0	.00	1.00	.96	.02	72	256.5	3.89
57	60	17	51.500	0	.00	1.00	.96	.02	60	184.5	3.58
58	43	16	35.000	1	.03	.97	.93	.03	42.5	124.5	3.56

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
59	26	3	24.500	0	.00	1.00	.93	.03	26	82	3.35
60	23	7	19.500	0	.00	1.00	.93	.03	23	56	2.87
61	16	7	12.500	0	.00	1.00	.93	.03	16	33	2.64
62	9	5	6.500	0	.00	1.00	.93	.03	9	17	2.62
63	4	1	3.500	0	.00	1.00	.93	.03	4	8	2.29
64	3	2	2.000	0	.00	1.00	.93	.03	3	4	2.00
65	1	1	.500	0	.00	1.00	.93	.03	1	1	2.00

Life Table for life expectancy from birth for first reports from 1981-2009 who had not died by 2008 or died in 2008 stratified by age at first report
Aged 45+ at first report

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
45	497	5	494.500	0	.00	1.00	1.00	.00	497	6206.5	12.55
46	492	3	490.500	1	.00	1.00	1.00	.00	491.5	5709.5	11.64
47	488	15	480.500	1	.00	1.00	1.00	.00	487.5	5218	10.86
48	472	29	457.500	0	.00	1.00	1.00	.00	472	4730.5	10.34
49	443	29	428.500	0	.00	1.00	1.00	.00	443	4258.5	9.94
50	414	16	406.000	1	.00	1.00	.99	.00	413.5	3815.5	9.40
51	397	31	381.500	0	.00	1.00	.99	.00	397	3402	8.92
52	366	28	352.000	0	.00	1.00	.99	.00	366	3005	8.54
53	338	37	319.500	0	.00	1.00	.99	.00	338	2639	8.26
54	301	37	282.500	0	.00	1.00	.99	.00	301	2301	8.15
55	264	21	253.500	0	.00	1.00	.99	.00	264	2000	7.89
56	243	26	230.000	0	.00	1.00	.99	.00	243	1736	7.55
57	217	22	206.000	0	.00	1.00	.99	.00	217	1493	7.25
58	195	27	181.500	1	.01	.99	.99	.01	194.5	1276	7.03
59	167	18	158.000	1	.01	.99	.98	.01	166.5	1081.5	6.84
60	148	19	138.500	0	.00	1.00	.98	.01	148	915	6.61
61	129	21	118.500	0	.00	1.00	.98	.01	129	767	6.47
62	108	12	102.000	0	.00	1.00	.98	.01	108	638	6.25
63	96	10	91.000	0	.00	1.00	.98	.01	96	530	5.82
64	86	11	80.500	0	.00	1.00	.98	.01	86	434	5.39
65	75	13	68.500	0	.00	1.00	.98	.01	75	348	5.08
66	62	15	54.500	0	.00	1.00	.98	.01	62	273	5.01
67	47	14	40.000	0	.00	1.00	.98	.01	47	211	5.28

(Current year of age at 31.12.2008 or at death in 2008) Interval Start Time	**(Pop)** Number Entering Interval	**(Censored - live at 25.9.09)** Number Withdrawing during Interval	**lx** Number Exposed to Risk (Like Person yrs) - (=C-(0.5*D))	**dx** Number of Terminal Events in 2008 (Deaths)	**qx (=dx-lx)** Proportion Terminating	**px (=1-qx)** Proportion Surviving	**Cumulative Px** (=for I 37, H37*H36) Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	**Lx** (Pop - deaths) + half deaths	**Tx** (cumulative years lived by those over that time)	**ex** (Mean additional years to be lived at that time)
68	33	5	30.500	0	.00	1.00	.98	.01	33	164	5.38
69	28	4	26.000	0	.00	1.00	.98	.01	28	131	5.04
70	24	8	20.000	0	.00	1.00	.98	.01	24	103	5.15
71	16	2	15.000	0	.00	1.00	.98	.01	16	79	5.27
72	14	2	13.000	0	.00	1.00	.98	.01	14	63	4.85
73	12	3	10.500	0	.00	1.00	.98	.01	12	49	4.67
74	9	1	8.500	0	.00	1.00	.98	.01	9	37	4.35
75	8	4	6.000	0	.00	1.00	.98	.01	8	28	4.67
76	4	1	3.500	0	.00	1.00	.98	.01	4	20	5.71
77	3	0	3.000	0	.00	1.00	.98	.01	3	16	5.33
78	3	0	3.000	0	.00	1.00	.98	.01	3	13	4.33
79	3	1	2.500	0	.00	1.00	.98	.01	3	10	4.00
80	2	0	2.000	0	.00	1.00	.98	.01	2	7	3.50
81	2	0	2.000	0	.00	1.00	.98	.01	2	5	2.50
82	2	1	1.500	0	.00	1.00	.98	.01	2	3	2.00
83	1	1	.500	0	.00	1.00	.98	.01	1	1	2.00

Appendix 8 Calculated SMR values

Table A8.1 Data for fig 6.2 (using reference population as 1989 HPS HIV prevalent patients)

	1989	1998	2001	2004	2007
95% Confidence limit		105.113	54.488	41.030	14.538
Female SMR	100	80.003	39.761	30.708	13.349
95% Confidence limit		54.894	25.033	20.386	12.159
95% Confidence limit		67.826	44.081	22.812	10.705
Male SMR	100	58.646	37.506	18.906	10.429
95% Confidence limit		49.467	30.931	15.000	10.153

Table A8.2 Data for fig 6.3 (using reference population as Scottish population 2001)

	1989	1998	2001	2004	2007
95% Confidence limit	4169.477	996.912	394.918	268.257	117.477
Female SMR	2539.947	645.833	240.575	169.546	68.151
95% Confidence limit	910.417	294.754	86.231	70.835	18.825
95% Confidence limit	1801.356	629.379	351.943	168.016	91.525
Male SMR	1386.835	489.060	269.969	123.737	65.627
95% Confidence limit	972.314	348.742	187.995	79.459	39.728

Appendix 9 Cause of death coding procedures in detail

To translate the 191 ICD10 codes used by HPS the full ICD10 list of 12024 codes with text descriptions was obtained from GROS and compared alongside the HPS codes used. The translation method for seven codes that could not at first be matched was to use the first 2 or 3 numbers to get the higher level diagnosis, and in one case correct a clear transposition error, (Y375) after consultation with supervisor, checking with HPS as above and with the WHO version of ICD10 was as table A9.1 below:

Table A9.1 Codes translated from ICD10 (HPS) to ICD10 (GROS)

ICD10 HPS to translate	Translated to ICD10 GROS
B249	B24
B2071	B207
E9289	E928
N9070	N907
N9916	N991
N9941	N994
Y375	Y357

Two ICD9 HPS codes could not be matched: 9941 and 9598. ICD10 came in 1994, but ICD9 codes were still being used by GROS coders well after that.

Primary cause of death coding

Although underlying cause was the starting point, the primary cause of death was identified from all six code positions. Diagnoses might link, for example if the first diagnosis was ‘HIV disease resulting in other specified conditions’, and the only other specified condition was ‘Unspecified acute lower respiratory infection ‘ in position 4 then the position 4 was the COD. In some cases the only diagnosis was HIV without any indication of what the HIV led to, in that case (and only that case) HIV was listed as the cause of death. Where trauma or suicide was a cause of death it occurred in the last position on a number of occasions, but was always taken as the primary cause over the other causes.

In other cases two possible codes could have been the primary cause of death – in that case the code in the earlier position was taken as the primary cause, unless:

1. the later was an infectious disease in which case it trumped a neoplasm as a primary cause, or
2. an earlier code indicated a specific choice for a later code. For example a case where the first code was B201 HIV disease resulting in other bacterial infections, then 2. unspecified HIV, 3. unspecified anaemia, 4. unspecified heart failure, 5. unspecified chronic bronchitis and 6. asthma, then primary cause of death was taken to be chronic bronchitis.

Drugs and alcohol as a primary COD

Drug or alcohol dependence alone was not considered a primary COD unless the only one recorded. Drug dependence was considered the primary cause of death if both it and deficiency of cell-based immunity were specified. 2860-2869 ('coagulation defects') and 8750 ('Contaminated substance transfused or infused') were taken as the primary COD only if no other option, but were taken as primary rather than 2791 ('Deficiency of cell mediated immunity') if the latter occurred too.

Hepatitis as a primary COD

If viral hepatitis B or C or any hepatitis was mentioned with cirrhosis or chronic liver disease then the cirrhosis or liver disease was taken as the primary cause of death if in position 1 to 4, otherwise the hepatitis was taken as the cause. If there was another infection or cancer in the first three positions it was taken rather than HCV as COD. If a condition was a consequence of HCV (such as liver failure) then HCV was taken as the primary cause, unless there was another more specific cause such as cirrhosis. Similarly for respiratory failure and heart failure, if another disease causing the failure was named. If a pneumothorax was likely causally related to another chest condition (e.g. pneumocystosis) then the related condition was taken as the primary cause. These refinements generally did not affect broader diagnostic groups (below) for primary codes.

Diagnostic groups

The lists of ICD9 and ICD10 codes and descriptions were assigned one of 31 groups for analysis (ICD9 first). The 8000 -9999 ICD9-CM codes were grouped in two

groups as firstly suicide, possible suicide or self harm (inc. by poisoning) (few of these) and secondly as 'other trauma inc. accidents (inc. accidental poisoning))'.

In classifying diagnoses into groups, the ICD10 HIV resulting in … codes were grouped under the condition resulted in rather than under HIV.

The face validity of the groupings was checked with a medical practitioner (CJ). Codes in all six positions were recoded to the relevant group for each death. The primary cause of death was also recoded. The original codes were retained. Both primary cause and each of the five other diagnostic positions were allocated to 31 broad diagnostic groups (which were later used to create broader groups of primary cause of death for AIDS and non-AIDS deaths analyses). In this way a common basis for analysis was created from the different coding structures used in ICD9 and ICD10. A list of the diagnostic groups is in Appendix 3, and broader groups in Appendix 6.

Hepatitis and AIDS coding

Four discrete groups were identified:

A. AIDS related (no Hep)
B. AIDS related (with Hep co-infection
C. Non AIDS (no Hep)
D. Non AIDS with hep co-infection

The Centre for Disease Control definition[11] was used to decide which diagnoses were AIDS defining, and this was additionally interpreted through medical practitioner input (CJ). The interpretation included the following:

- Intracranial and intraspinal abscess was AIDS defining since it was most likely caused by Toxoplasmosis (on the CDC list).
- Other protozoal diseases were also taken as AIDS defining as most likely caused by cryptococcosis (also on the CDC list).
- Slow virus infection of the CNS if prior on the death certificate to an HIV diagnosis, then AIDS defining.

- Other non-arthropod-borne viral diseases of the CNS – implies Toxoplasmosis, so AIDS defining.
- Aspergillosis was not included as AIDS defining since it was dropped from the CDC case definition in 1984 due to lack of evidence that either CD4 lympopenia was a predisposing factor, or that there was any significant increase in the incidence of invasive aspergillosis among HIV-infected patients (Schaffner 1984)[200] None of the five patients who had a mention of Aspergillosis died before 1991.

Primary cause of death was coded as whether AIDS or not, according to an adapted CDC definition,[11] which followed the precedent of Babiker et al (2000).[113] Babiker used only first part of the CDC definition, meaning deceased people with a latest CD4 cell count below 200 but without any of the recognised AIDS defining diagnoses were not coded as an AIDS death. All causes in any of the six positions were classified as whether AIDS or not.

AIDS coding procedures

Both primary cause and other causes were classified as whether AIDS defining. After consultation with a medical practitioner (CJ) the HIV codes in ICD10 were taken to be AIDS defining as they all referred to another condition associated with the HIV. The one exception was B24 'HIV unspecified', which was taken as AIDS defining only if it was the only code entered, since that situation could be assumed to be an omission on the part of the doctor or coder. This approach was taken for the equivalent ICD9 code (0449), but the other ICD9 HIV codes were treated in the same way described above. That applied for ICD9 codes for both HIV 'causing' or only 'with' a specified condition, on the grounds that the accompanying condition had been specified.

The ICD9 coded data also contained a group of codes about cell-mediated immunity deficiency that did not occur in the ICD10 data. These (occurring only as 2791, 2793 and 2799) were coded as HIV.

To merge the deaths data with the treatment data, the translated death codes data was used as a lookup table using case reference number as the key. The single file resulting contained both treatment and deaths data and was saved as values for import to SPSS for analysis. As an audit trail of the methods used for translation the

translation spreadsheet with the comparison of GROS and ISD codes descriptions was retained.

Appendix 10 SPSS syntax for selected analyses

Mean age at five time points.

Explanation: with age at each time point calculated in advance, the following syntax analysed mean age of the live patients at each time point.

```
USE ALL.
COMPUTE filter_$=(Firstrptby30_6_1989 = 1 &Deadby30June1989 = 0).
VARIABLE LABEL filter_$ 'Firstrptby30_6_1989 = 1 &Deadby30June1989 = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
MEANS TABLES=agetime1 BY PC_AIDS
  /CELLS MEAN COUNT STDDEV.

USE ALL.
COMPUTE filter_$=(Firstrptby30_6_1998 = 1 &Deadby30June1998 = 0).
VARIABLE LABEL filter_$ 'Firstrptby30_6_1998 = 1 &Deadby30June1998 = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
MEANS TABLES=agetime2 BY PC_AIDS
  /CELLS MEAN COUNT STDDEV.

USE ALL.
COMPUTE filter_$=(Firstrptby30_6_2001 = 1 &Deadby30June2001 = 0).
VARIABLE LABEL filter_$ 'Firstrptby30_6_2001 = 1 &Deadby30June2001 = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
MEANS TABLES=agetime3 BY PC_AIDS
  /CELLS MEAN COUNT STDDEV.

USE ALL.
COMPUTE filter_$=(Firstrptby30_6_2004 = 1 &Deadby30June2004 = 0).
VARIABLE LABEL filter_$ 'Firstrptby30_6_2004 = 1 &Deadby30June2004 = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
MEANS TABLES=agetime4 BY PC_AIDS
  /CELLS MEAN COUNT STDDEV.

USE ALL.
COMPUTE filter_$=(Firstrptby30_6_2007 = 1 &Deadby30June2007 = 0).
VARIABLE LABEL filter_$ 'Firstrptby30_6_2007 = 1 &Deadby30June2007 = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
MEANS TABLES=agetime5 BY PC_AIDS
  /CELLS MEAN COUNT STDDEV.
```

Allocating age groups to prevalent patients for age standardisation

Explanation: This is an SPSS syntax example for allocating age group at the reference date and sex groups for patients who died in 1997, 1998 or 1999. Age group at each reference date was pre-calculated. This syntax was adapted to allocate age groups for those who died 1988-1990, 2000-2002, 2003-2005, and 2006-2008.

```
USE ALL.
COMPUTE filter_$=(Diedin1997_1998_1999=1).
VARIABLE LABEL filter_$ 'Diedin1997_1998_1999=1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
CROSSTABS
  /TABLES=age_atdeaththreegroups BY Sex
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

Appendix 11 Demographic group by HAART era of first report and whether alive or deceased at 25.9.09

Whether deceased at 25.9.09		HAART Era of HPS first report				Total
		Pre-HAART	Early HAART	Late HAART	Ultra active ART	
Alive at 25.9.09	Female	348	110	274	572	1304
	Male	913	320	536	1207	2976
	Total	1261	430	810	1779	4280
Deceased	Female	290	10	12	8	320
	Male	1127	61	46	39	1273
	Total	1417	71	58	47	1593

Whether deceased at 25.9.09		HAART Era of HPS first report				Total
		Pre-HAART	Early HAART	Late HAART	Ultra active ART	
Alive at 25.9.09	0-19	131	19	29	49	228
	20-24	298	37	91	177	603
	25-34	580	204	337	667	1788
	35-44	195	124	244	591	1154
	45+	57	46	109	295	507
	Total	1261	430	810	1779	4280
Deceased	0-19	137	1	3	2	143
	20-24	366	4	2	2	374
	25-34	545	20	9	11	585
	35-44	252	31	24	11	318
	45+	117	15	20	21	173
	Total	1417	71	58	47	1593

Whether deceased at 25.9.09		HAART Era of HPS first report				Total
		Pre-HAART	Early HAART	Late HAART	Ultra active ART	
Alive at 25.9.09	Asian	4	10	13	38	65
	Black	91	62	246	558	957
	Mixed or other	3	3	12	12	30
	White	1103	320	477	964	2864
	No information or missing	60	35	62	207	364
	Total	1261	430	810	1779	4280
Deceased	Asian	2	0	1	2	5
	Black	23	0	10	8	41
	Mixed or other	5	1	0	0	6
	White	1376	67	44	37	1524
	No information or missing	11	3	3	0	17
	Total	1417	71	58	47	1593

Whether deceased at 25.9.09		HAART Era of HPS first report				Total
		Pre-HAART	Early HAART	Late HAART	Ultra active ART	
Alive at 25.9.09	Blood/Tissue TR	10	3	9	4	26
	Haemo	36	2	0	1	39
	Heterosex	290	182	409	912	1793
	IDU	420	46	52	71	589
	IDU+MSM	13	2	8	3	26
	MSM	466	177	307	699	1649
	Other	2	3	3	2	10
	MTC (vertical)	13	9	14	22	58
	Unknown	11	6	8	65	90
	Total	1261	430	810	1779	4280
Deceased	Blood/Tissue TR	19	1	2	2	24
	Haemo	48	0	0	0	48
	Heterosex	168	15	26	18	227
	IDU	707	22	9	4	742
	IDU+MSM	22	2	1	0	25
	MSM	427	26	15	19	487
	Other	3	0	1	0	4
	MTC (vertical)	15	0	2	1	18
	Unknown	8	5	2	3	18
	Total	1417	71	58	47	1593

Appendix 12 Unadjusted ORs for Transmission group in reference to BTT

	Exp(B)	95% C.I.for EXP(B)		Sig.
		Lower	Upper	
Transmission Route (referred to Blood/tissue transfer)				.000
Haemophilia	1.333	.664	2.678	.419
Heterosexual	.137	.077	.243	.000
IDU	1.365	.775	2.402	.281
IDU+MSM	1.042	.477	2.274	.918
MSM	.320	.182	.562	.000
Other	.433	.120	1.567	.202
Mother to child (Vertical)	.336	.156	.724	.005
Unknown	.217	.102	.459	.000
Constant	.923			.777

Appendix 13 Proportions of deaths from AIDS and with AIDS including COD unknown in denominator

Table A13.1 Proportion of AIDS defining and non AIDS defining primary cause of death by HAART era (inc. COD unknown)

Whether Primary COD was AIDS defining	Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra active ART (%)	Total (%)	p for $\mathcal{X}^2$ for trend
Death from AIDS (primary cause)	705 (49.8)	21 (29.6)	23 (39.7)	16 (34)	**765 (34)**	
Not death from AIDS	389 (27.5)	16 (22.5)	10 (17.2)	11 (23.4)	**426 (26.7)**	**<0.001**
COD unknown	323 (22.8)	34 (47.9)	25 (43.1)	20 (42.6)	**402 (25.2)**	
Total	**1417 (100)**	**71 (100)**	**58 (100)**	**47 (100)**	**1593 (100)**	

Table A13.2 Proportion of AIDS defining and non AIDS defining as any cause of death by HAART era (inc. COD unknown)

Whether Any COD was AIDS defining	Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra active ART (%)	Total (%)	p for $\mathcal{X}^2$ for trend
Death with AIDS (any cause)	818 (57.7)	31 (43.7)	32 (55.2)	25 (53.2)	**906 (56.9)**	
Not death with AIDS	276 (19.5)	6 (8.5)	1 (1.7)	2 (4.3)	**285 (25.2)**	**<0.001**
COD unknown	323 (22.8)	34 (47.9)	25 (43.1)	20 (42.6)	**402 (25.2)**	
Total	**1417 (100)**	**71 (100)**	**58 (100)**	**47 (100)**	**1593 (100)**	