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

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1. Background

There is an increasing population living with an HIV positive diagnosis in Scotland.[1] Highly Active Antiretroviral Therapy (HAART) was implemented in developed countries around 1996. It helped boost CD4 cell count, CD4 cells fight HIV. A small literature review for this study found evidence of reduced mortality and improved survival and life expectancy in developed countries including Scotland[2] since the introduction of HAART.

Within this overall improving picture generally, there was some evidence that the proportion of non-AIDS or non-HIV related deaths had increased.[3;4] There was some evidence that the proportion of certain non-AIDS defining cancers linked to HPV infection increased,[5] and that AIDS defining infections were the main cause of AIDS-related deaths.[6] HAART, HIV and lifestyle factors have been linked to increasing atherosclerosis in the HIV+ population,[7-12] but evidence was mixed on any increase in incidence or mortality with CVD events in patients with HIV.[13] Thus the case for CVD risk screening specifically targeted to HIV+ people was inconclusive.

There was evidence that older people with HIV were an increasing proportion of the HIV positive population,[14;15] It was thought they had greater co-morbidity and more toxic effects from HAART,[14] and lower survival and higher AIDS incidence than younger.[16] Their adherence to treatment, though generally good could be compromised in circumstances such as cognitive impairment and drug interaction.[17] Older peoples' virologic response to HAART tended to be more rapid than in younger people, but immunologic (CD4 count) responses were the same or worse than in younger people.[18] Late or non diagnosis was a possible issue in older people,[19] and potentially the largest remediable factor in preventing HIV related death.

Scottish causal evidence for the effectiveness of HAART was implicit in a dose response relationship between number of ART drugs and increased CD4 cell count.[2] In Scotland, as elsewhere, the proportion of transmission of HIV by IDUs fell.[20] Heterosexual and overseas transmission increased.[20] HCV morbidity has recently emerged as an issue, as there is evidence of higher mortality in HCV/HIV co-infection than for HCV infection alone.[21;22] Scottish research reports a 'Scottish effect' on wider health involving poor life expectancy and excess mortality by international comparisons,[23-25] but there is little recent work comparing life expectancy with HIV in Scotland with elsewhere.

2. Aims

The aims of this study were to analyse demographic, mortality, survival, life expectancy and cause of death trends in the population testing positive for HIV in Scotland over four HAART eras of patient first report from 1981 to 2009, and to set their implications in the context of wider research.

3. Methods

Data from a national HPS Scottish dataset was merged with cause of death data collected by HPS through multiple methods including data linkage. The data was checked, coded and recoded to establish diagnostic categories and give a set of groups to analyse for demographic trends, survival times and mortality at different time points and over four eras of patient first report that were decided in relation to phases of the development of HAART. These were pre-HAART (1981-1996), early HAART (1997-1999), late HAART (2000-2003), and ultra-active HAART (2004-2009). Statistical analysis then used descriptive and multivariate methods including:

1. for survival time, Kaplan Meier plots,
2. for hazard of death, Cox's proportional hazards model,
3. for adjusted odds of death, binomial logistic regression,
4. for age adjustment, standardised mortality ratios,
5. and a current complete life table to enable comparison of life expectancy with other studies of other HIV positive populations.

4. Results for people living with HIV in Scotland

4.1 Demographics

4.1.1 Overall

Nearly three quarters of cases overall (from 1981-2009) were male. Deceased patients were statistically significantly more likely to be male, but male patients were statistically significantly older than females at first report. Overall, age at first report was early thirties. For the prevalent population, mean age increased over time from 29.4 (1989) to 42.1 (2009). The proportion aged 45+ at first report increased from 7% pre-HAART to 17% in ultra-active HAART.

4.1.2 Trends

Other demographic changes between eras of HAART in people first reporting with HIV in each era are shown in the table below:

Variable	Pre-HAART %	Ultra active HAART %
injection drug use transmission	42	5
heterosexual transmission	17	51
MSM transmission	33	39
female patients	24	32
non-white patients	5	20
heterosexual people	38.5	68.5

4.2 Mortality trends

Annual Mortality peaked in 1995 at 10%, age standardised mortality reduced consistently from 1989. SMR dropped more slowly for women than men initially but caught up by 2007. Compared to 1989, (=100 for each sex) age adjusted SMR in 2007 was 13.3 for women and 10.4 for men. The average annual mortality rate per 1,000 persons for 2003-2008 was 9.64, compared to 53.48 in the period 1981-1996. The overall CMR for 1981-2008 per 1,000 person years was 31.65.

4.3 Cause of death trends

The proportion of all deaths (including COD unknown) that were AIDS-related fell to percentages in the mid fifties in the post HAART eras of first report. This held both for any cause and for primary cause only. The trend was statistically significant ($p<0.001$) when the pre-HAART era was included, but not statistically significant for post-HAART alone. When 402 cases with COD unknown were excluded there was no trend for either increasing or decreasing proportion of deaths with an AIDS

defining primary cause, but there was a statistically significant trend (p<0.001) for an increasing proportion to die with at least one AIDS defining condition as any cause of death (including primary cause) (see table below).

Death with AIDS (any COD) as a proportion of total deaths (COD unknown excluded)

Pre-HAART (%)	Early HAART (%)	Late HAART (%)	Ultra active ART (%)
818/1094 (74.8)	31/37 (83.8)	32/33 (97)	25/27 (92.6)

p<0.001

Infections were the largest proportion of AIDS related deaths by the ultra-active era.

4.4 Survival trends

The Kaplan Meier plots and proportional hazards models showed that survival time increased at statistically significant levels for patients first reporting over each of the four eras. For those who died **of** AIDS (primary cause) survival time reduced by era, with each era showing a lower survival time than the last, this was especially clear for the survival curves for those dying **with** AIDS (any cause). For those dying with hepatitis there were significant differences in survival times by era, but while survival time for those with any hepatitis condition as a cause of death reduced slightly in the early and late HAART eras, in the ultra active HAART era the early indications were that the survival curve tracked that for the pre-HAART era.

4.5 Unadjusted odds of death (each category compared against all other cases)

Over the whole time period, unadjusted odds of death were calculated using simple cross tabulations. By risk (transmission) group, IDU transmission showed highest odds for (OR 5.464 (95% CL 4.791-6.231, p for χ^2<0.001) compared to all other) and lowest odds were for heterosexual transmission (OR 0.230, 95%CL 0.198-0.269, p for χ^2 <0.001 compared to all other). For ethnic categories, odds of death for white people were highest (OR 10.92 (95% CL 8.509-14.015, p for χ^2<0.001) in comparison to all others), and for age groups odds of death were highest for the 20-24 age group (OR 1.9 (95% CL 1.6-2.2, p for χ^2<0.001) in comparison to all others). Males had statistically significantly greater unadjusted odds of death than females, OR 1.74 (95% CL 1.52-2.0, p for χ^2<0.001).

Odds of death with AIDS (any position) were highest for heterosexual transmission (OR 2.587 (95% CL 1.589-4.212, p for χ^2<0.001) in comparison to all others) and lowest for transmission related to haemophilia (OR 0.360 (95% CL 0.183-0.710, p for

X^2<0.002) in comparison to all others), while odds of death with hepatitis (any position) were highest for IDU transmission (OR 5.132 (95% CL 2.942-8.954, p for X^2<0.001) in comparison to all others) and lowest for MSM transmission (OR 0.133 (95% CL 0.053-0.331, p for X^2<0.001) in comparison to all others).

4.6 Comparative trends in unadjusted and adjusted odds of death

To compare adjusted and unadjusted ORs validly, the unadjusted ORs are reported in comparison to the reference categories used for the adjusted ORs. For sex and ethnicity the unadjusted ORs were as reported above. They were a valid comparison because both the adjusted and unadjusted ORs were binomial variables (white compared to all others for ethnicity). The unadjusted OR for year of age at first report was calculated by running a logistic regression model including only that variable (The unadjusted OR for age (years) was 0.983 (0.977-0.988, p<0.001, HL test p<0.001). Unadjusted OR per unit of CD4 count was calculated in a similar way (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 each transmission category was calculated in relation to BTT as that was the reference category for the adjusted OR. The highest unadjusted OR in reference to BTT was for IDU transmission , (OR 1.365, (95% CL 0.775-2.402, p<0.281)), and the lowest was heterosexual transmission (OR 0.137, (95% CL 0.077-0.243, p<0.001)).

Adjusted odds ratios of death (from a binomial logistic regression model including selected covariates) were statistically significant for era of HAART first report, time already survived, age group, ethnicity, transmission route, and earliest CD4 count group. All three eras of HAART first report had statistically significant and continually decreasing ORs for death in comparison to pre-HAART.

Comparison of selected adjusted and unadjusted ORs for death (Overall 1981-2009)

Variable	Reference category	Unadj'd OR	p	Adjusted OR	p
Males	Females	1.74	<0.001	1.023	<0.916
White	Non white	10.92	<0.001	5.653	<0.001
Year of age at first report (ascending)	Previous year of age at first report	0.983	<0.001	1.071	<0.002
Unit of Earliest CD4 count (ascending)	Previous unit of earliest CD4 count	0.998	<0.001	0.999	<0.003
IDU transmission	BTT transmission	1.365	<0.281	<0.001	<0.002
Heterosexual transmission	BTT transmission	0.137	<0.001	0.012	<0.040

First reported in Ultra-active HAART era	First reported pre-HAART	0.024	<0.001	<0.001	<0.001

The adjusted ORs for males became non statistically significantly greater than for females when the effects of the other variables were taken into account. That does not mean that men had a lower risk of death than the unadjusted OR gave, it means their increased risk of death was not simply owing to being men, but was also associated with other variables such as, for example, being more likely to be diagnosed pre-HAART, more likely to be have transmission of HIV through the IDU route. Risk behaviours are, however, associated with male sex. On the other hand, IDU transmission, which did not have a statistically significantly greater unadjusted OR for death than BTT, was a statistically significantly lower risk than BTT when adjusted for the other factors, suggesting IDU transmission was highly influenced by other factors (perhaps any or all of age, sex, white ethnicity and era of first report). OR for year of age at first report in comparison to previous year changed from being a protective factor (unadjusted) to being a risk factor (adjusted).

4.7 Changes in adjusted risk factors by era of first report.

The adjusted OR for males in comparison to females increased to 1.8 in the ultra active HAART era in comparison to pre-HAART, but remained NS. The adjusted OR for white people in comparison to non-white reduced in the ultra-active era to 3.4, but was not statistically significantly different from non-white risk. The IDU transmission route was statistically significantly less risky than BTT in ultra-active HAART (OR 0.035, p<0.029), but this difference had been NS pre-HAART. Earliest CD4 count increased its statistical significance between pre-HAART to ultra-active HAART, with lower risk of death for each additional unit (OR 0.987, p0.003). Year of age at first report in comparison to previous year of age at first report became not statistically significant in the ultra-active HAART period, from being very significant pre-HAART (OR 2.133, p<0.002).

4.8 Life expectancy

Life expectancy from a current complete life table at current year of age = 20 was 23 years in 2008.

5. Discussion

As elsewhere, the annual mortality rate peaked in Scotland in 1995-96. The age adjusted SMR fell more consistently than AMR over five selected time points 1981-2009. The increasing proportion aged over 44 at first report (see results, sec. 4.1) suggested later infection and perhaps also late diagnosis. In combination with possible later infection, increasing proportions infected through (especially hetero) sexual contact suggested a need for health protection and promotion interventions for older age groups. Other studies suggested MSM transmission remained more likely to be found in older than in younger adults.[15]

Increasing survival times, in combination with increasing mean age of the prevalent population (see results sec. 4.1) suggested a need to focus on age associated health issues in planning health service provision. The reduction in the proportion infected through the IDU route in the face of increasing numbers of IDUs generally suggested targeted health protection interventions can make a difference in preventing transmission of HIV.

There were unexpected variations in survival time between HAART eras of first report for those dying with and of AIDS. A possible explanation of the lower survival without AIDS in the pre-HAART era could have been an increased likelihood of death then from acute conditions not classified as AIDS-related, such as suicide, trauma and some conditions involving CVD, which resulted in more rapid demise than from AIDS in individuals experiencing them. A double selection effect from stigma-sensitive individuals delaying their own first report may have also resulted in more rapid death from or with AIDS after first report as the eras followed on. The increasing proportion aged over 44 at first report the later the era may have been related to increased vulnerability to rapid demise following an AIDS related infection.

HAART era of first report was even more highly significantly related to risk of death after adjustment for other risk and demographic factors. When survival time was taken into account the risk of death reduced further by era. Since the number of therapies was not adjusted for as a covariate in the logistic regression, it is possible that the increased survival with era of HAART was related to the introduction of triple (and quadruple) therapy. There may also have been a HAART associated improvement in mental health in connection with the reduction in suicide and trauma deaths post-HAART.

Adjusted ORs for death for males and for IDUs were not statistically significant, indicating that era or age effects at first report may have accounted for most of the unadjusted ORs for these. The age-adjusted SMR for women, in comparison to their mortality in 1989, dropped more slowly for than for men after the introduction of HAART, but almost caught up by 2007.

The significantly greater OR of being deceased remained higher for white in comparison to non-white people even after adjustment for the other factors included in the logistic regression model, suggesting the non-white population benefitted from specific protective factors, or that they had not been exposed to risk for as long. CMRs calculated per 100,000 person years were lower by a factor of ten than CMRs calculated per 100,000 persons.

The increased risk of death with year of age at first report found in my study accorded with the more recent wider literature suggesting decreased survival[26] and increased mortality[27] for older people testing positive for HIV.

The absence of any pre-post HAART decline in the proportion of deaths (with known cause) that were with or from AIDS disagreed with findings from other countries.[6] There was a statistically significantly increasing trend over eras of first report in the proportion of deaths that included an AIDS-related condition as any cause. Survival time in those who died from AIDS (i.e. had a primary diagnosis of AIDS) had reduced in comparison to non-AIDS post HAART. This study did not find an increase in the proportion of non-AIDS deaths post HAART, but concerns about increased morbidity from non-AIDS defining conditions remained.

Despite increasing survival and reducing mortality, the life expectancy with HIV in Scotland was at the lower end of estimates for other locations found from abridged life tables elsewhere in the literature.[28-32] The lower LE could partly reflect the so called 'Scottish'[25] or 'Glasgow'[23;24] effects, and possibly associated dietary, alcohol, tobacco and drug use factors.

6. Conclusions

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.

7. Recommendations

7.1 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[33])
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.[34]

7.2 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,[35] 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.

7.3 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.

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