

Chapter 9: Changing mortality in HIV positive people

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HIV Related Deaths

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"In this world nothing can be said to be certain, except death and taxes." Benjamin Franklin 1789.

It is hard to believe the improved outlook over the past two decades for someone diagnosed with HIV. The first two patients I looked after with HIV in 1986 had been infected in the Middle East by unscreened blood transfusions. Both had late stage AIDS and died within a couple of months. When I arrived in Liverpool a year later, the average survival of a person coming to hospital with an 'AIDS-defining condition' such as pneumocystis pneumonia (PCP) was about nine months, with a maximum of two years. In those early years, our inpatient service resembled a haematology unit looking after patients with leukaemia in the 1960s, and counsellors for patients also had to support staff, especially the nurses, who were befriending and supporting young people with a dismal and stigmatising infection. These people had recurrent hospital admissions with very poor survival prospects, and our staff attended too many funerals. Many patients at diagnosis cashed in their life insurance or remortgaged their possessions to enjoy life to the full for a brief period before an expected rapid and irretrievable decline.

Then came the huge changes, accelerating with the advent of triple antiretroviral therapy in the mid 1990s, as well as improved multidisciplinary care and specific advances in treatment and prevention of infections and tumours associated with HIV. The mortality for HIV positive adults in developed countries has fallen from about 30% per year to about 2%, and this is certainly our local experience^{1,2}. The average survival of a patient starting antiretroviral therapy is now probably 20 years or more. A recent Danish study³, presented in 2006 at the XVI International AIDS Conference in Toronto, suggests that someone infected with HIV at 25 would live to 63.9 years, compared to an HIV negative person living to 76.2 years. More than half my clinic patients are now just regular clinic attendees like in any 'chronic disease' such as high blood pressure, diabetes and so on – a quick clinical review and a chat, appropriate blood tests, prescription, back to work and return to clinic in three to six months – unthinkable 10 years ago.

So far so good – but not everyone has benefited. We still see people who have not been diagnosed as HIV positive and/or who have not received modern treatment. There are often many reasons for this, especially for the substantial number of people arriving from sub-Saharan Africa and other parts of the world where HIV is very common. Such patients can arrive at hospital desperately ill with several HIV related problems, but can do well if they survive the initial difficult months. However, there is still too much denial and risk-taking among others, leading to delays in seeking testing and sometimes treatment. Like all treatment centres, we took part in a recent national audit of deaths of HIV positive persons by the British HIV Association (BHIVA). This showed that about a third of all deaths had nothing to do with HIV (trauma, heart attacks etc). However, the four next most common issues implicated in deaths were shocking: patient was diagnosed too late for effective treatment; under care but had untreatable complication; treatment ineffective due to poor adherence; or chose not to receive treatment. All these are issues that health care workers and patients can work together to improve. In addition, we need to encourage the normalisation of HIV testing in health care settings, as the diagnosis is still considered too late by generalists and HIV tests are still regarded as 'special'.

So how to prepare for the inevitable, even if it is delayed? My headmaster gave weekly lessons on 'life skills' to school leavers and one was on dying and probate – he taught that it was the worst form of bad manners to die without leaving a will, even if you had virtually nothing to leave anyone. In the context of HIV, everyone who is positive should also have a clearly defined and legally recognised next of kin, and should also consider who might need a power of attorney to make decisions on their behalf if they become too ill (physically or mentally) to do so for themselves. The contents of a living will should be discussed with these individuals and of course all these details need to be communicated to any clinics or health care staff involved. In the past, I have seen too many tragic scenes in which parents or other legal next of kin have thrown out or disregarded the opinions and needs of recently bereaved partners who had no legal status.

Confidentiality of diagnosis is as important after death as before, but is sometimes difficult to maintain. This is particularly difficult when a body needs repatriation – current regulations require that a positive body be flown in a lead lined coffin (at a cost of about £3500 to the family). This massive cost and unusual mode of transport make attempts to preserve confidentiality look pretty ridiculous.

Finally, we continue to learn from our patients even after death. In Liverpool, we have been privileged over the years to perform autopsies on about half of the HIV positive patients who die in hospital. This is a very emotive issue for both staff and relatives, but is incredibly useful. It allows us (usually) to confirm that we have been doing the right thing for the right diagnosis, but in up to half of our cases, also reveals unexpected or new findings. This helps us to change our approach to diagnosis and management of future patients, and we thank all those involved for allowing us to help other HIV positive people in this way.

Introduction

At the start of the UK's HIV/AIDS epidemic in 1982, AIDS wards were common sights in hospitals and HIV was an acute illness with only palliative care available to treat the effects of the disease. At that time it was realistic to make provisions for one's death as there was very little in the way of treatment for HIV/AIDS and life expectancy was short (as it is often the case in terminal illness). Early in the HIV epidemic the majority of people died in hospitals. However, by the late 1980s services were more able to fulfil patients' death plans and there was a move away from dying in hospitals to hospices and at home, with increased support from community services⁴. Prior to the widespread availability of antiretroviral therapy (ART), studies showed that by 1996 HIV contributed between 0.5% (in rural localities) to 20% (in one London authority) of years of potential life lost among 15-44 year olds⁵. Another study carried out prior to the widespread use of ART, examined survival since time of seroconversion. Using data from Europe, North America and Australia the collaborative group on AIDS incubation and HIV survival assessed the effect of exposure category on the AIDS incubation period and HIV-1 survival⁶. They also examined whether age at seroconversion varied with exposure category and time since seroconversion. Results showed that mortality and AIDS increased with time since seroconversion, and also with age from seroconversion. Median survival was 12.5 years at ages 15-24 and 7.9 years at ages 45-54. Similar results were found for the development of AIDS, however, no effect of exposure category on survival was found. There was a variation between AIDS onset and exposure category; for heterosexuals the median time to the development of AIDS was over 10 years and survival time was more than 11 years; the median time to the development of AIDS for men who have sex with men (MSM) was 10.8 years. The study also revealed a difference in mortality between the sexes with a female to male ratio of 0.77, however, this was no longer significant when adjusted for exposure category. A 10 year increase in age at seroconversion was associated with a 1.47 fold increase in the risk of death and a 1.32 fold increase in the risk of developing AIDS. Therefore, being older and older age at seroconversion were predictors of mortality⁶.

Since the introduction and widespread use of ART in 1996, the number of HIV deaths in the UK have fallen dramatically and continue to decline⁷. The current HIV treatment and care available has led to HIV becoming a more manageable, long-term chronic illness. Soon after widespread use of HAART (highly active antiretroviral therapy) was introduced, reductions in HIV/AIDS mortality rates were seen (from 15.6 to 2.7 per 100 person years of follow up between 1994 and 2001)⁸. Later studies have shown that although there has been a dramatic decrease in the number of people dying of AIDS, from 1994 there have been increases in the number of deaths from other causes, such as hepatitis and myocardial infarction and the number of deaths pre-AIDS. Findings showed that there was an estimated 47% increase in each calendar year in the odds of dying with no AIDS defining illness. There was an 18% decrease in the crude odds of dying after three or more AIDS defining illnesses (no change for one or two), and there was an overall decrease in the number of deaths in the HIV positive population under investigation⁹. Exploring cause of death within the three HAART eras (pre, early and late) studies showed a decrease in HIV-1 related deaths among some patients in the late-HAART era compared to the early HAART era. This reduction was not seen for patients with CD4 counts of between 51 and 200 cells/mm³. The combined incidence of AIDS and death has declined in patients in the EuroSIDA study (from 1994-2002). The incidence of AIDS declined further in the late HAART era, leading to the conclusion that the introduction of HAART has resulted in low morbidity and mortality rates across Europe¹⁰. Similar results were found in a UK study¹¹ which examined the opportunity for receiving HAART modelled over three time periods; pre multiple therapies (pre-1995), multiple reverse-transcriptase inhibitor therapy (September 1995 – March 1996), and multiple therapy including protease inhibitors (April 1996 onwards). Findings showed that survival rates improved significantly among female heterosexuals and men who have sex with men (MSM) when multiple therapies including protease inhibitors became available.

One study focused solely upon women with, and at risk of, HIV¹². The study included 2,059 HIV positive women and 569 women at risk from HIV (defined by baseline characteristics similar to HIV positive women in the USA) enrolled from 1994 – 1995. Death was classed as due to AIDS or non-AIDS from death certificates and CD4 counts. Findings show that all-cause and AIDS-related mortality for HIV positive women decreased from 1995 to April 1997 (due to ART). All-cause mortality decreased at a rate of 26% per year and AIDS-related mortality decreased at a rate of 39% per year among HIV positive women. Multivariate models adjusting for age, race and other factors, showed that depressive symptoms and past injecting drug use were associated with death from non-AIDS causes in HIV positive women. In unadjusted analyses hepatitis C and a history of injecting drug use was a significant risk factor for non-AIDS related death due to liver disease, drug overdose and malignancy among HIV infected women. Studies argue that HIV positive drug users benefit less than other groups from HAART. Since the availability of HAART the risk of AIDS and death for injecting drug users (IDUs) decreased by 28% and 36% respectively, which is less than has been recorded for other risk groups¹³. This may be due to worse general health or because of the increased levels of deprivation among IDUs, subsequent limited access to health care and hence late entry into services¹⁴.

A recent study of 387 deaths in Britain showed that one in three causes of death in the HIV positive population were not related to HIV¹⁵. Cancer (non-HIV related as well as HIV related cancers), not HIV, is one of the main causes of death among this population. National guidance issued by the British HIV association recommends prescribing ART before the CD4 count falls below 200 cells/mm³ to prevent disease progression. They also recommend that for patients with counts above this, disease progression should be considered and therapy should commence provided that the patient wishes it¹⁶. Evidence has shown that life expectancy for patients on ART is not significantly different to that of the general population¹⁷, and the transition of HIV from an acute terminal disease to a chronic manageable disease is represented in the pattern of care in the North West of England which is now primarily via outpatient care¹⁸.

This study aims to explore any significant differences in these mortality data in the time periods 1996-2000 and 2001-2005 to determine whether differences in the demographics of these populations exist. These time periods were chosen in order to explore the differences in mortality between early and late HAART eras. Analysis aims to compare deaths in the HIV positive population with those of the general North West population to observe changes over time and differences in demography. Analysis was also carried out between the total population accessing treatment and care within the two time periods under investigation in order to predict mortality and compare any changes. Differences between individuals who died within a year of diagnosis and those who died a year or more after diagnosis were also explored. This allows those most at risk of mortality to be identified in order to inform prevention interventions and add to the body of knowledge on HIV mortality using comprehensive data collected from an entire regional population.

Methodology

This study aims to explore the pattern of HIV mortality in the North West of England. It compares the adjusted death rates of the HIV positive population in 1996-2000 and 2001-2005 to those of the general population. It also looks at the differences between those infected via heterosexual sex and through sex between men (MSM). Sex and age specific death rates were calculated using the following equation $\{ASDR = D_{NW} * 100,000/P_{NW}\}$ where ASDR is Age Specific Death Rate, D_{NW} is the number of occurrences of crude death in North West for each age group and P_{NW} is the relevant population in the North West for age group¹⁹. Following this, age-adjusted death rates were calculated using the age specific rates multiplied by the European Standard Population in the corresponding age groups given the numbers of deaths that would be 'expected' in the European Standard Population if it experienced North West age-specific rates. The sum of the 'expected' deaths divided by 100,000 gives the directly age-standardised rate per 100,000 for the North West region²⁰. To generate the expected deaths, the ASDR were converted into a proportion by dividing the rate by 100,000 and multiplying them by the European standard population groups by age²¹. Age-adjusted death rates (AADR) were calculated using the following equation $\{AADR = \text{Expected Death Rate} * 100,000 / \text{Standard Population}\}$ ²⁰.

Ten years of mortality data were extracted from the HIV/AIDS Monitoring Unit's treatment and care database, based at the Centre for Public Health, Liverpool John Moores University. Where possible, missing data were matched to the new diagnosis database and were queried with treatment centres (e.g. date of death, date first positive, stage at death) in an attempt to update them. Missing data were completed where it could be reliably estimated (using date first seen and date last seen). Missing data accounted for 40% of date first positive fields and 3% of date died fields. After estimating missing data, 73% of dates first seen and 100% of dates died were completed. Age was calculated for the general HIV positive population by age at the end of the treatment year, however age for those who died was calculated using the date of death. Ethnicity data and information on level of antiretroviral therapy were not collected by the system until 1997 and 1998 respectively. The missing data were queried with treatment centres wherever possible. This method of data extraction ensured that all deaths reported to the HIV/AIDS Monitoring Unit have been included in these analyses. Occasionally there are delays in deaths being reported when individuals have not attended for HIV treatment and care in the period in which they died and the information takes time to filter through to the surveillance system. Therefore, the number of deaths reported here sum to more than all those reported in the annual North West HIV reports. Univariate and multivariate analyses were carried out to determine demographic differences and predictors of mortality between the two populations. Length of time from diagnosis to death was also analysed to identify any differences in the population surviving less than one year after diagnosis.

Results

Figure 9.1 shows age specific death rates for the HIV positive population and the North West general population in 1996-2000 and 2001-2005. These data show a drop in HIV death rates, however they remain higher than those of the general population. There was a large proportion of deaths among HIV cases aged 60 plus in the period of 1996-2000, however, the age specific death rate fell most significantly in the 25-54 age group, as can be seen by the smaller confidence intervals. Age adjusted death rates (AADR) were calculated (total column in figure 9.1) and the comparison shows that during the period of 1996-2000 the HIV AADR was almost four times higher than those of the general North West population. However, HIV AADRs dropped to a much lower rate in 2001-2005 (1,650 compared to the general population figure of 1,025), 61% higher than the North West general population AADR.

Age-specific death rates for the MSM and heterosexual HIV positive populations were calculated (data not shown). They showed that the highest death rates were in the 45 to 60 plus age groups for the period of 1996-2000 and in the 60 plus age group for the period of 2001-2005. The heterosexual HIV infected population age-specific death rates for North West region showed that the death rates were highest in the 60 plus age group at 9,091/100,000 and the 55-59 age group at 4,242/100,000 for the period of 1996-2000 and 2001-2005 respectively. AADRs were also calculated separately for MSM and heterosexual (data not shown). The AADR for MSM was 3,695/100,000 and 1,390/100,000 for the period of 1996-2000 and 2001-2005 respectively and was 3,925/100,000 and 1,645/100,000 for 1996-2000 and 2001-2005 respectively for the HIV positive heterosexual population. It is evident that the AADR for MSM is lower than the AADR for heterosexuals in both periods.

Table 9.1 shows cause of death for periods 1996-2000 and 2001-2005. Unknown cases were removed prior to analyses, however both periods had similar proportion of completed data. Findings show no significant difference in cause of death. However this could change if all causes were known. Although not significant there is an increase in the proportion of people who died of *Pneumocystis Carinii* Pneumonia (PCP), Tuberculosis (TB) and Pneumonia, Myocardial Infarction (MI), liver disease or others and slight increase in the proportion of deaths from accidents, suicides or murder.

Table 9.2 shows the yearly mean number of outpatient days, day cases, inpatient episodes, inpatient days and home visits for those who died between 1998-2005. It also shows mean CD4 count and viral load where these data were available and mean age at death. Data show fluctuating numbers of outpatient attendances, consistently low numbers of day cases and consistently high numbers of inpatient days. Table 9.2 indicates ill-health and shows that those who died have consistently low CD4 counts and consistently high viral loads. Furthermore, the data show the average age at death remained in the early to mid 40s.

Table 9.3 presents data on sex, ethnicity, infection route, stage of HIV disease, age group, level of antiretroviral therapy, age at diagnosis, infected abroad, indices of multiple deprivation and residency status for those alive and dead 1996-2000 and 2001-2005. For 1996-2000 ethnicity, infection route, stage of HIV disease, age group, level of ART, age at diagnosis and infection abroad were significant. A significantly higher proportion of those who died in 1996-2000 compared to the proportion in the general HIV population had an unknown ethnicity (33.5% compared to 10%), had AIDS (69% compared to 27.9%), were not taking ART (87.2% compared to 65%), were aged 45 and over (28.5% compared to 19.9%), had an unknown age at diagnosis (47.5% compared to 16.6%) and had unknown information for infected abroad (40.5% compared to 15.5%). Compared to the general population in treatment and care in 2001-2005, the HIV positive population who died had a higher proportion of white people (76.5% compared to 66.4%), IDUs (10.9% compared to 2.5%), people with AIDS (73.3% compared to 21.9%), people not taking ART (47.5% compared to 36.4%), individuals aged 45 or over (38.4% compared to 23.3%), diagnosed at aged 45 or over (24.9% compared to 11.5%) and UK nationals (83.7% compared to 75.9%). For 2000-2005 infected abroad and IMD were not significant variables. Sex was not significant for either time period.

Table 9.4 predicts mortality in 1996-2000 and 2001-2005. After adjusting for all other variables in both time periods, route of infection, stage of HIV disease, ethnicity, age at diagnosis, level of antiretroviral therapy were all predictors of mortality. Sex and age group at death were not predictors of mortality in either time period. Deprivation and residency status were not predictors of mortality in 2001-2005. In both time periods IDUs and heterosexuals were at higher risk of mortality than those infected via MSM, those whose stage was AIDS (and unknown in 1996-2000) were at higher risk of mortality than those who were symptomatic, and those aged 60 and over at diagnosis were at a higher risk of mortality than those aged 0-24 years at diagnosis.

A two-way ANOVA was carried out to determine whether or not there was a significant difference between the length of time from diagnosis to death for men and women and for different routes of infection for both time periods (data not shown). Findings revealed that there was a significant difference in route of infection ($F_{2,334}=10.1$, $P<0.001$). MSM and those with other or unknown routes of infection (includes IDU, blood/tissue and mother to child transmission routes) were significantly more likely to be diagnosed for longer than those infected via heterosexual sex. However, there was no significant difference between the time periods under investigation ($F_{1,334}=0.1$, $P=0.726$) and no interaction between the periods and route ($F_{2,334}=0.2$, $P=0.818$). Analysis by sex showed no significant difference in sex ($F_{1,336}=2.8$, $P=0.093$). However, men were slightly more likely than women to have been infected with HIV for longer prior to death (4.9 years compared to 3.5 years in 1996-2000 and 4.7 years compared to 3.6 years in 2001-2005). Overall, there was no difference between the two periods examined ($F_{1,336}=0.006$, $P=0.941$) and no interaction between time periods and sex ($F_{1,336}=0.2$, $P=0.877$). Analyses on sex and age at death showed that men were significantly older when they died ($F_{1,459}=24.3$, $P<0.001$). This is reflected in the mean age at death for the two time periods, with a mean age 41 and 34.8 for men and women respectively in 1996-2000, and a mean age of 44.4 and 37.6 for men and women respectively in 2001-2005. This relationship is significantly different between the two time periods ($F_{1,459}=5.5$, $P=0.020$), however there is no interaction between the periods and sex ($F_{1,459}=0.4$, $P=0.847$).

Table 9.5 shows further analysis carried out on those who died in 1996-2000 and 2001-2005 where data were available on length of infection from time of diagnosis to death (53% and 93% respectively). Univariate analyses on data from 1996-2000 reveal that those infected abroad and those of black/other/unknown ethnicity were more likely to survive less than one year after diagnosis. Findings from the univariate analyses carried out on the 2001-2005 population show that those of black/other/unknown ethnicity, infected through heterosexual sex, diagnosed with AIDS, not taking antiretroviral therapy, infected abroad and either an asylum seeker/other or unknown were more likely to survive less than a year after diagnosis.

Table 9.6 identifies predictors of surviving less than a year. After multivariate adjustment, no factors were significant in 1996-2000. ART and infection abroad were significant predictors in the 2001-2005 population. However, after multivariate analysis residency status was no longer significant.

Figure 9.1: North West age specific death rates with total age adjusted death rates for the HIV positive and the general population (error bars represent 95% confidence intervals), 1996-2005

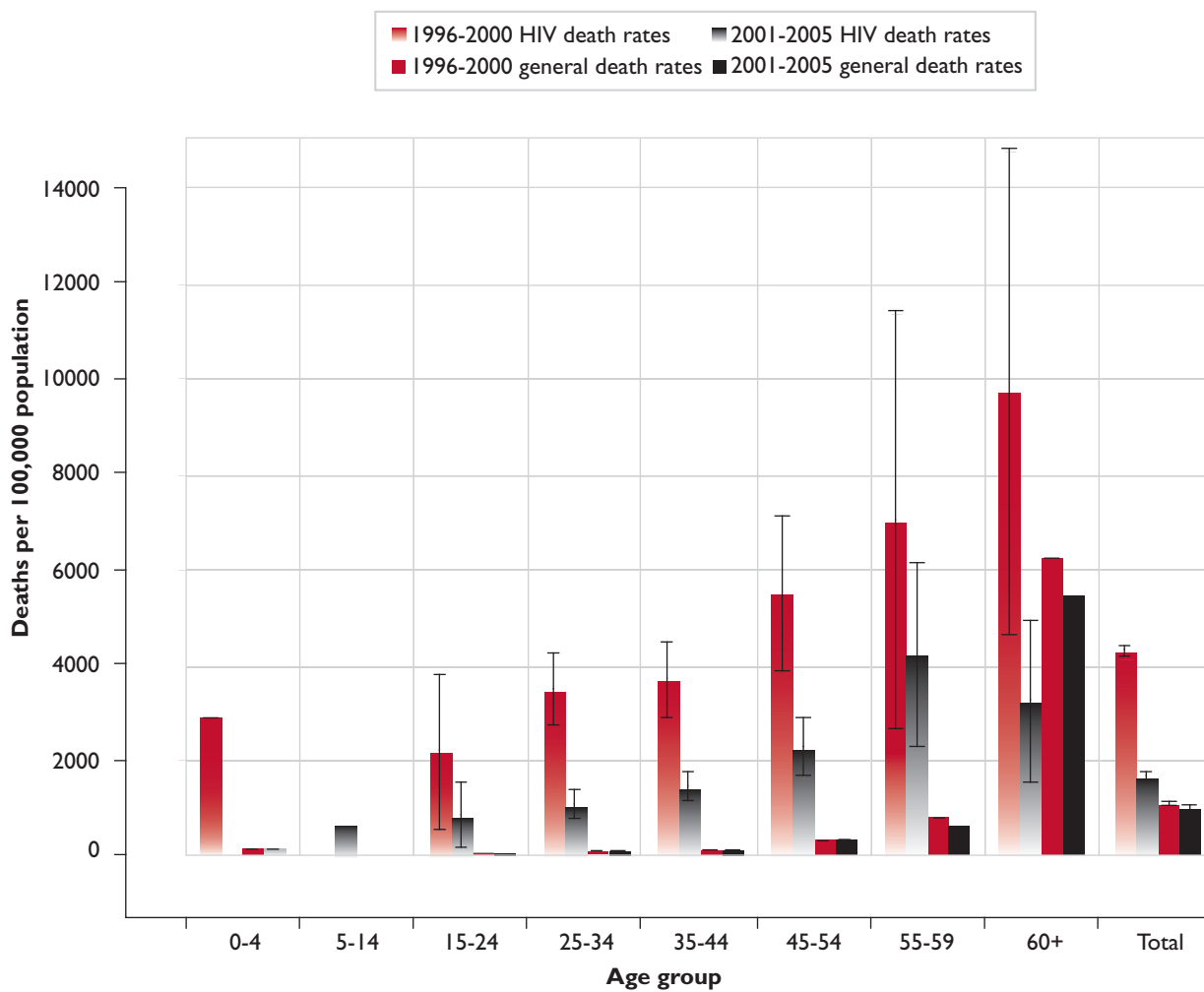


Table 9.1: Cause of death by death period

Cause of death+	Death Period		Total	Chi Square
	1996-2000	2001-2005		
Accident/murder/suicide	10 (15.9%)	14 (17.3%)	24 (16.7%)	P=0.118
MI/liver diseases/others	11 (17.5%)	20 (24.7%)	31 (21.5%)	5.872
Cancer/virus	29 (46%)	22 (27.2%)	51 (35.4%)	df=3
PCP/TB/Pneumonia	13 (20.6%)	25 (30.9%)	38 (26.4%)	

+Unknowns have been excluded

Table 9.2: Treatment and care use, health tests and age at death, 1998-2005

	1998		1999		2000		2001		2002		2003		2004		2005	
	n	Mean (min/max)	n	Mean (min/max)	n	Mean (min/max)	n	Mean (min/max)	n	Mean (min/max)	n	Mean (min/max)	n	Mean (min/max)	n	Mean (min/max)
Treatment and care use																
Outpatient episodes	39	1.05 (0-17)	38	5.39 (0-24)	33	3.36 (0-15)	39	6.44 (0-41)	42	5.55 (0-52)	43	4.19 (0-27)	51	2.41 (0-14)	46	3.48 (0-14)
Day cases		0.13 (0-4)		0.53 (0-6)		0.06 (0-1)		1.77 (0-24)		0.40 (0-8)		0.91 (0-19)		0.61 (0-17)		1.04 (0-41)
Inpatient episodes		0.21 (0-3)		2.21 (0-12)		1.45 (0-8)		1.67 (0-7)		1.43 (0-6)		1.44 (0-6)		1.31 (0-9)		1.83 (0-12)
Inpatient days		3.74 (0-77)		26.39 (0-164)		22.91 (0-116)		32.38 (0-168)		21.31 (0-181)		23.63 (0-107)		16.86 (0-132)		28.37 (0-160)
Home visits*								2.10 (0-43)		4.07 (0-22)		3.60 (0-45)		0.90 (0-16)		0.26 (0-7)
Health tests																
CD4 (min/max)	7	263 (7-1210)	7	278 (70-450)	17	184 (8-630)	15	172 (10-389)	30	227 (2-670)	17	255 (6-1200)	20	232 (1-820)	25	249 (1-1553)
Viral load (min/max)	6	539970 (8815-750001)	8	16138 (102-75001)	13	246781 (50-1000001)	15	56019 (49-346000)	31	117929 (49-644000)	16	49443 (49-240000)	18	196337 (49-1810000)	22	71054 (39-230000)
Age at death																
Mean age (min/max)	39	39.3 (27.3-63)	38	45.4 (26.5-74.3)	33	43.4 (29.8-62)	39	42.5 (5.7-69.9)	42	42.7 (24.6-69.8)	43	43.5 (23.8-79.1)	51	43.2 (20.4-73.2)	46	42 (23.2-70.8)

*Home visit data were collected from 2001 only

Table 9.3: Sex, ethnicity, infection route, stage of HIV disease, age group, level of antiretroviral therapy, age at diagnosis, infected abroad, indices of multiple deprivation and residency status for HIV positive people alive and dead, 1996-2000 and 2001-2005

	1996-2000				2001-2005					
	Alive	Dead	Total (100%)	Chi square	Alive	Dead	Total (100%)	Chi square		
Sex					P=0.966					P=0.291
Male	1737 (89.2%)	211 (10.8%)	1948	<0.1	3616 (95.5%)	170 (4.5%)	3786	1.1		
Female	253 (89.1%)	31 (10.9%)	284	df=1	1288 (96.2%)	51 (3.8%)	1339	df=1		
Ethnicity					P<0.001					P<0.001
White	1628 (91.7%)	148 (8.3%)	1776	108.5	3254 (95.1%)	169 (4.9%)	3423	16.4		
Black	163 (92.6%)	13 (7.4%)	176	df=2	1399 (97.5%)	36 (2.5%)	1435	df=2		
Other/Unknown	199 (71.1%)	81 (28.9%)	280		251 (94%)	16 (6%)	267			
Route of infection					P=0.055					P<0.001
MSM	1338 (90.2%)	146 (9.8%)	1484	7.6	2594 (96.4%)	97 (3.6%)	2691	61.2		
Injecting drug use	114 (83.8%)	22 (16.2%)	136	df=3	121 (83.4%)	24 (16.6%)	145	df=3		
Heterosexual	386 (88.7%)	49 (11.3%)	435		1921 (96%)	80 (4%)	2001			
Other/Unknown	152 (85.9%)	25 (14.1%)	177		268 (93.1%)	20 (6.9%)	288			
Stage of HIV disease					P<0.001					P<0.001
Asymptomatic	525 (98.9%)	6 (1.1%)	531	311.6	2274 (99.3%)	17 (0.7%)	2291	322.6		
Symptomatic	883 (95.8%)	39 (4.2%)	922	df=3	1489 (97.7%)	35 (2.3%)	1524	df=3		
AIDS	556 (76.9%)	167 (23.1%)	723		1072 (86.9%)	162 (13.1%)	1234			
Unknown	26 (46.4%)	30 (53.6%)	56		69 (90.8%)	7 (9.2%)	76			
Age group					P=0.002					P<0.001
0-24	117 (93.6%)	8 (6.4%)	125	16.6	308 (97.8%)	7 (2.2%)	315	31.5		
25-34	669 (89.4%)	79 (10.6%)	748	df=4	1487 (97%)	46 (3%)	1533	df=4		
35-44	809 (90.4%)	86 (9.6%)	895		1966 (95.9%)	83 (4.1%)	2049			
45-59	348 (86.4%)	55 (13.6%)	403		992 (93.3%)	71 (6.7%)	1063			
60+	47 (77%)	14 (23%)	61		151 (91.5%)	14 (8.5%)	165			
Level of ART					P<0.001					P=0.001
None*	1293 (86%)	211 (14%)	1504	48.9	1785 (94.4%)	105 (5.6%)	1890	13.5		
Triple or less	555 (95.4%)	27 (4.6%)	582	df=2	2259 (96.1%)	92 (3.9%)	2351	df=2		
Quadruple or more	142 (97.3%)	4 (2.7%)	146		860 (97.3%)	24 (2.7%)	884			
Age at diagnosis					P<0.001					P<0.001
0-24	294 (93.9%)	19 (6.1%)	313	155.9	755 (97.8%)	17 (2.2%)	772	55.3		
25-34	746 (94.6%)	43 (5.4%)	789	df=5	2013 (96.4%)	75 (3.6%)	2088	df=5		
35-44	437 (93%)	33 (7%)	470		1332 (95.3%)	66 (4.7%)	1398			
45-59	157 (88.2%)	21 (11.8%)	178		506 (92.2%)	43 (7.8%)	549			
60+	25 (69.4%)	11 (30.6%)	36		60 (83.3%)	12 (16.7%)	72			
Unknown	331 (74.2%)	115 (25.8%)	446		238 (96.7%)	8 (3.3%)	246			
Infected abroad					P<0.001					P=0.122
No	1217 (91.8%)	108 (8.2%)	1325	90.6	2489 (95.7%)	113 (4.3%)	2602	4.2		
Yes	464 (92.8%)	36 (7.2%)	500	df=2	1720 (96.3%)	67 (3.7%)	1787	df=2		
Unknown	309 (75.9%)	98 (24.1%)	407		695 (94.4%)	41 (5.6%)	736			
National IMD quintiles										P=0.624
Least deprived					120 (96%)	5 (4%)	125	3.5		
Fourth					221 (94.4%)	13 (5.6%)	234	df=5		
Third					312 (97.2%)	9 (2.8%)	321			
Second					659 (96.2%)	26 (3.8%)	685			
Most deprived					2277 (95.6%)	104 (4.4%)	2381			
Unknown					1315 (95.4%)	64 (4.6%)	1379			
Residency status										P<0.001
UK					3723 (95.3%)	185 (4.7%)	3908	16.8		
Asylum seeker/ Other migrant+					884 (98.1%)	17 (1.9%)	901	df=2		
Unknown					297 (94%)	19 (6%)	316			
Total	1990	242	2232		4904	221	5125			

*ART was not collected until 1997, thus for the purpose of this analysis individuals presenting prior to this period are counted as not taking ART
+The asylum seeker/Other migrant category includes refugees, temporary visitors, overseas students, migrant workers, dependents and others

Table 9.4: Logistic regression to predict mortality in 1996-2000 and 2001-2005

	1996-2000				2001-2005			
	n	Adj OR 95.0% C.I. (-/+)	df	P value	n	Adj OR 95.0% C.I. (-/+)	df	P value
Sex			1	0.700			1	0.322
Male	1948	Reference category			3786	Reference category		
Female	284	0.896 (0.513-1.565)			1339	1.259 (0.798-1.984)		
Age group			4	0.404			4	0.257
0-24	125	Reference category			315	Reference category		
25-34	748	1.547 (0.590-4.056)		0.375	1533	0.719 (0.255-2.030)		0.533
35-44	895	1.054 (0.391-2.837)		0.917	2049	0.575 (0.191-1.734)		0.326
45-59	403	1.290 (0.445-3.737)		0.639	1063	0.554 (0.166-1.851)		0.337
60+	61	1.065 (0.200-5.681)		0.941	165	0.122 (0.018-0.831)		0.032
Route of infection			3	0.015			3	<0.001
MSM	1484	Reference category			2691	Reference category		
Injecting drug use	136	2.380 (1.319-4.293)		0.004	145	5.091 (2.889-8.972)		<0.001
Heterosexual	435	1.743 (1.030-2.950)		0.039	2001	1.683 (1.052-2.695)		0.030
Other/Unknown	177	1.321 (0.742-2.350)		0.344	288	1.831 (0.992-3.382)		0.053
Stage of HIV disease			3	<0.001			3	<0.001
Asymptomatic	531	Reference category			2291	Reference category		
Symptomatic	922	3.844 (1.597-9.255)		0.003	1524	6.160 (3.339-11.366)		<0.001
AIDS	723	29.655 (12.832-68.534)		<0.001	1234	52.285 (29.830-91.641)		<0.001
Unknown	56	39.729 (14.620-107.960)		<0.001	76	8.050 (3.104-20.879)		<0.001
Ethnicity			2	0.023			2	0.005
White	1776	Reference category			3423	Reference category		
Black	176	0.734 (0.351-1.536)		0.412	1435	0.353 (0.189-0.659)		0.001
Other/Unknown	280	1.711 (1.111-2.634)		0.015	267	0.784 (0.413-1.485)		0.455
Age at diagnosis			5	0.001			5	0.007
0-24	313	Reference category			772	Reference category		
25-34	789	0.747 (0.394-1.415)		0.371	2088	1.566 (0.776-3.159)		0.210
35-44	470	1.061 (0.510-2.205)		0.874	1398	2.232 (1.009-4.937)		0.047
45-59	178	1.515 (0.617-3.723)		0.365	549	3.731 (1.451-9.597)		0.006
60+	36	5.207 (0.937-28.942)		0.059	72	24.775 (3.873-158.491)		0.001
Unknown	446	2.204 (1.132-4.292)		0.020	246	1.091 (0.394-3.027)		0.866
Level of ART			2	<0.001			2	<0.001
No therapy	1504	Reference category			1890	Reference category		
Triple or less	582	0.328 (0.207-0.521)		<0.001	2351	0.193 (0.134-0.278)		<0.001
Quadruple or more	146	0.156 (0.055-0.445)		0.001	884	0.100 (0.059-0.169)		<0.001
Infected abroad			2	0.079			2	0.727
No	1325	Reference category			2602	Reference category		
Yes	500	0.605 (0.368-0.997)		0.049	1787	1.067 (0.693-1.642)		0.770
Unknown	407	1.093 (0.726-1.647)		0.669	736	1.197 (0.770-1.863)		0.424
National IMD quintiles							5	0.270
Least deprived					125	Reference category		
Fourth					234	1.821 (0.561-5.915)		0.318
Third					321	0.778 (0.227-2.670)		0.690
Second					685	1.267 (0.423-3.791)		0.673
Most deprived					2381	1.680 (0.595-4.743)		0.327
Unknown					1379	1.321 (0.460-3.790)		0.605
Residency status+							2	0.266
UK national					3908	Reference category		
Asylum seeker/ Other migrant*					901	0.579 (0.293-1.146)		0.117
Unknown					316	1.005 (0.546-1.852)		0.986

+Residency status was not collected until 2000. *The asylum seeker/Other migrant category includes refugees, temporary visitors, overseas students, migrant workers, dependents and others

Table 9.5: Sex, ethnicity, Route of infection, stage, infected abroad, ART and residency status for those dying within one year of diagnosis compared to those dying a year or more after diagnosis, 1996-2000 and 2001-2005

	Survival time 1996-2000				Survival time 2001-2005			
	<1 year	≥1 year	Total	Chi Square	<1 year	≥1 year	Total	Chi Square
Sex				P=0.851				P=0.086
Male	28 (84.8%)	81 (86.2%)	109 (85.8%)	<0.1 df=1	48 (68.6%)	108 (79.4%)	156 (75.7%)	3.0 df=1
Female	5 (15.2%)	13 (13.8%)	18 (14.2%)		22 (31.4%)	28 (20.6%)	50 (24.3%)	
Ethnicity				P=0.003				P=0.002
White	21 (63.6%)	82 (87.2%)	103 (81.1%)	8.9 df=1	43 (61.4%)	111 (81.6%)	154 (74.8%)	10.0 df=1
Black/Other/Unknown	12 (36.4%)	12 (12.8%)	24 (18.9%)		27 (38.6%)	25 (18.4%)	52 (25.2%)	
Route of infection				P=0.071				P=0.003
MSM	12 (36.4%)	54 (57.4%)	66 (52%)	5.3 df=2	21 (30%)	71 (52.2%)	92 (44.7%)	12.0 df=2
Heterosexual	12 (36.4%)	18 (19.1%)	30 (23.6%)		37 (52.9%)	40 (29.4%)	77 (37.4%)	
Other/Unknown	9 (27.3%)	22 (23.4%)	31 (24.4%)		12 (17.1%)	25 (18.4%)	37 (18%)	
Stage of HIV disease				P=0.322				P=0.026
Asymptomatic/ Symptomatic/Unknown	11 (33.3%)	23 (24.5%)	34 (26.8%)	1.0 df=1	12 (17.1%)	43 (31.6%)	55 (26.7%)	5.0 df=1
AIDS	22 (66.7%)	71 (75.5%)	93 (73.2%)		58 (82.9%)	93 (68.4%)	151 (73.3%)	
Infected abroad				P=0.026				P<0.001
No	13 (39.4%)	62 (66%)	75 (59.1%)	7.3 df=2	20 (28.6%)	82 (60.3%)	102 (49.5%)	20.6 df=2
Yes	9 (27.3%)	16 (17%)	25 (19.7%)		35 (50%)	31 (22.8%)	66 (32%)	
Unknown	11 (33.3%)	16 (17%)	27 (21.3%)		15 (21.4%)	23 (16.9%)	38 (18.4%)	
Antiretroviral therapy								P=0.008
No ART					44 (62.9%)	59 (43.4%)	103 (50%)	7.0 df=1
ART					26 (37.1%)	77 (56.6%)	103 (50%)	
Residency status								P<0.001
UK					48 (68.6%)	124 (91.2%)	172 (83.5%)	17.7 df=2
Asylum seeker/Other					10 (14.3%)	7 (5.1%)	17 (8.3%)	
Unknown					12 (17.1%)	5 (3.7%)	17 (8.3%)	
Total (100%)	33	94	127		70	136	206	

Table 9.6: Logistic regression to predict living less than one year after HIV diagnosis

	1996-2000				2001-2005			
	n	Adj OR 95.0% C.I. (-/+)	df	P value	n	Adj OR 95.0% C.I. (-/+)	df	P value
Sex			1	0.323			1	0.690
Male	109	Reference category			156	Reference category		
Female	18	0.491 (0.120-2.010)			50	1.210 (0.473-3.096)		
Route of infection			3	0.344			3	0.110
MSM	66	Reference category			92	Reference category		
Injecting drug use	14	1.067 (0.214-5.308)		0.937	23	0.546 (0.158-1.891)		0.340
Heterosexual	30	2.556 (0.757-8.628)		0.131	77	1.043 (0.363-2.993)		0.938
Other/Unknown	17	2.493 (0.678-9.168)		0.169	14	3.870 (1.069-14.012)		0.039
Stage of HIV disease			1	0.259			1	0.298
Asymptomatic/Symptomatic/Unknown	34	Reference category			55	Reference category		
AIDS	93	0.559 (0.203-1.537)			151	1.535 (0.685-3.442)		
Ethnicity			1	0.078			1	0.606
White	103	Reference category			154	Reference category		
Black/Other/Unknown	24	2.601 (0.897-7.543)			52	0.758 (0.264-2.173)		
Infected abroad			2	0.082			2	0.002
No	75	Reference category			102	Reference category		
Yes	25	2.528 (0.738-8.659)		0.140	66	5.871 (2.234-15.427)		<0.001
Unknown	27	3.204 (1.093-9.387)		0.034	38	2.362 (0.895-6.236)		0.083
Age group			2	0.433			2	0.081
0-34	44	Reference category			51	Reference category		
35-54	65	0.507 (0.176-1.466)		0.210	126	0.960 (0.437-2.110)		0.919
55-60+	18	0.524 (0.126-2.186)		0.375	29	0.271 (0.078-0.939)		0.039
Antiretroviral therapy							1	0.018
No ART					103	Reference category		
ART					103	0.427 (0.211-0.865)		
Residency status							2	0.069
UK					172	Reference category		
Asylum seekers/Other migrants					17	1.545 (0.421-5.666)		0.512
Unknown					17	4.509 (1.246-16.313)		0.022

Discussion

The reduction in deaths in the HIV positive population has frequently been explored, especially since the advent of antiretroviral therapy (ART). However, analyses have not been carried out using a regional surveillance dataset. These analyses show that overall, the number of deaths in the North West's HIV positive population decreased dramatically between 1996-2000 and 2001-2005. However, age specific death rates in the HIV positive population remain higher than that of the North West's general population (figure 9.1), and the age adjusted death rate is higher for both periods. Thus, it is evident that the death rate in the HIV positive population, even in the modern era of ART (2001-2005), is significantly higher than in the general population.

The widespread use of antiretroviral therapies is commonly accepted to have led to the reduction in the number of HIV deaths. The findings from this study support the view that individuals not taking ART are more at risk of dying than those on ART regimens (tables 9.3 and 9.4). There were significantly more people taking ART in 2001-2005 than in previous years. However, at the time of death almost half of the individuals that died in 2001-2005 were not reported to be taking ART. There are a few possible reasons why patients with AIDS may not be taking ART, such as treatment non-adherence and treatment holidays, or a decision to come off treatment. For those with no treatment history we may assume that people who died in the earlier years may not have been able to access ART as this may have been prior to its widespread availability. For others, they may have been diagnosed too late in their illness to have benefited from the medication available or have been at a stage of HIV that did not require medication.

Individuals who died over the past ten years have, on the whole, been older than the general HIV positive population (table 9.3). The HIV positive population is aging and HIV is now recognised as a chronic disease as opposed to an acute illness. As such, it can no longer be assumed that people with HIV will necessarily die from a HIV related illness and; as table 9.1 shows, cause of death can be unrelated to HIV infection. Many causes of death remained unknown, and although there was an increase in the numbers of deaths from Pneumocystis Carinii Pneumonia (PCP), Tuberculosis (TB) and Pneumonia and Myocardial Infarction (MI), liver disease or others, there was no significant difference in the profile of death types between the two time periods studied. These data are supported by findings in other studies that showed the most frequent cause of non-HIV deaths as cardiovascular, hepatic, and pulmonary

disease, and non-AIDS malignancies in 2004²². Table 9.3 also shows that the majority of people with HIV in the North West die at a progressed stage of HIV disease with over three quarters having an AIDS defining illness at some time prior to their death. Mean CD4 count and viral loads (table 9.2) confirm this as they indicate that, where data were available, in the period prior to death individuals' health was poor, with low CD4 counts, relatively high viral loads and a greater use of inpatient care than any other type of care.

Chapter 4 shows that HIV is strongly linked to deprivation, with the prevalence of HIV over six times higher in the most deprived quintile compared to the least deprived, a higher ratio than that found for other chronic conditions²³. It follows that there are also many more deaths in the most deprived quintile than the least deprived (table 9.3). However, this chapter shows that the proportion of HIV positive people who died did not differ between deprivation quintiles (table 9.4).

There were increasing numbers of deaths in the female HIV positive population although the numbers of deaths in HIV positive women are much lower than in HIV positive men. This is understandable as historically the epidemic has primarily affected men. Despite this, the number of heterosexual women equalled the number of MSM nationally in 2001²⁴. However, this is a trend which has yet to be seen in the North West. The logistic regression analyses model in table 9.4 shows that sex was not a significant predictor of death, therefore HIV positive women are at equal risk of death as HIV positive men. An examination of the mean death rate for women showed that they were more likely to have been diagnosed for less time than their male counterparts and they were also more likely to be younger than men when they died. It is possible that this is due to late diagnosis of HIV. However, women are very often diagnosed during antenatal screening and are therefore more likely to be diagnosed at an earlier stage of their HIV infection. These findings are consistent with other studies. For example Lowndes et al.²⁵ conducted a study in Brazil which pointed to gender health inequalities and showed that women tended to die at relatively younger ages than men in all areas studied. An American study also concluded that the HIV prognosis for women was worse¹². However the women in these studies were frequently infected via IDU, which is not the case in this study, where the vast majority are infected via heterosexual sex. Heterosexuals reported to have died were also diagnosed more recently than those infected via MSM. The heterosexual population that died in both time periods was made up almost equally of men and women therefore it may be that those infected via this route are diagnosed later in their disease than others. One study conducted in France highlighted that young, heterosexuals who are newly diagnosed are more likely to die of opportunistic infections than any other cause of death. It maintains that opportunist infections remain a major cause of death in HIV-infected younger patients in the ART era, especially among patients recently diagnosed for HIV infection and who do not have access to care, as well as in long term infected patients where prophylaxis should be revisited²⁶. Overall, heterosexuals reported to have died in the North West are predominantly infected abroad, are evenly divided between both sexes and between white and black and minority ethnic groups. As the majority were infected abroad it may be that they were infected long before their actual diagnosis and not diagnosed until they were in the UK. The fact that the majority of the women reported to have died were also infected abroad and were predominantly black (51%) may indicate that they seroconverted long before diagnosis.

Further analyses of those who died have revealed a subgroup of people dying within a year of commencing care in the North West (tables 9.5 and 9.6). These findings are indicated in both time periods, however, data for the time period 2001-2005 are more reliable due to better completeness and additional information collected. The data in table 9.5 show that a high proportion of deaths occurred within a year of diagnosis (one third of all deaths in 2001-2005). Further examination of these data revealed cases where diagnosis and death had occurred simultaneously or within a very short period of each other. Individuals dying within a year of diagnosis were more likely to be black, heterosexual, not taking ART, suffering with AIDS, infected abroad and either an asylum seeker/other or unknown. After multivariate analyses, predictors of dying within one year of diagnosis were ART and infection abroad (table 9.6). Residency status was no longer a significant predictor of dying within one year of diagnosis and this may be due to the high number of people for whom residency status is unknown. An individual is likely to be reported as having and 'unknown' residency status where there is some doubt over their UK nationality and, considering that the majority of these unknown cases were heterosexual, infected abroad and diagnosed with AIDS it may well be the case that they were not UK nationals. These data show that individuals are presenting for treatment and care too late in their HIV disease for medical staff to find out their full personal details. They are certainly presenting too late in their disease to benefit sufficiently from the life prolonging treatments available.

It is clear that there are migrant populations in the North West in urgent need of both HIV health promotion and HIV treatment and these data reinforce the need for early diagnosis and swift provision of HIV treatment and care. The stigma and discrimination surrounding migrant populations may create hesitancy in accessing treatment and care. In addition, migrant populations tolerate the stresses of upheaval and dispersal and consequently seeking appropriate health care may not be the highest priority²⁷, especially to the primary caregivers, who are often women. This population may possibly contribute to the female mortality rate and explain the younger age at death as it may be due to young childbearing women foregoing medical care due to family demands. Current concerns surrounding free access to treatment and care for migrant populations serve to further stigmatise and endorse barriers to accessing treatment and care. However, concerns over people travelling from high prevalence countries abroad in order to access free HIV care have no basis; in fact, previous analyses have revealed that asylum seekers present to services at no later stage of HIV than non-asylum seekers and do not use services more (see chapter 8)²⁸. Looking at the general HIV positive population, no significant effect of residency status on mortality is apparent. It is only when deaths are considered separately and time between diagnosis and death is considered that an effect of late diagnosis becomes clear. However, there is a minority living in the UK for an indeterminate period of time who are either hesitant to seek

treatment and care until a very late stage of disease or who have been unable to access care, which raises wider issues regarding their general health care provision and pathways to services. It is primarily individuals infected abroad who are at most risk of dying within one year. This includes individuals from the UK as well as those from other countries. It is imperative that people are aware of the risks of HIV transmission in other high prevalence countries. People infected abroad are more likely to be heterosexual, and if they are UK nationals they may not necessarily consider themselves at risk of this particular sexually transmitted infection. The fact that the majority of individuals dying within a year of diagnosis are not taking ART means that they may be ignorant of their infection until it is too late. This may be because they do not fall into a traditional high risk group. Therefore it is important that those travelling abroad are aware of the risks of HIV transmission.

This analysis of deaths in the North West has highlighted the drop in death rate in the HIV positive population in the North West and shown that heterosexuals have a higher death rate than MSM after adjusting for any differences in the age structure of the population. However, the death rate in the North West HIV positive population remains significantly higher than in the general population. Analysis has also shown that men were significantly older than women at death and that prior to dying those infected via MSM and other/unknown routes of infection were significantly more likely to have been diagnosed for longer than those infected through heterosexual sex. Importantly, analysis has revealed a vulnerable subgroup of people at risk of dying less than a year after accessing care in the North West. The analysis presented here is limited by the lack of data on cause of death, age at diagnosis and accurate residential information and future analyses would be more robust if missing data could be collected to provide a more comprehensive picture. These data also emphasise the need for consultants to report deaths on the clinician reporting forms to the HIV/AIDS Monitoring Unit. Future, analyses need to be carried out to estimate the life expectancy of HIV positive people living in the North West of England.

To conclude, the numbers of new HIV infections continue to increase¹⁸ and with fewer deaths and an aging HIV positive population the risks of onward HIV transmission are higher than ever before. People infected with HIV are increasingly able to consider their infection manageable and continue to plan for a future including having children, working and travelling. However, very few studies have reviewed the effectiveness of HIV prevention interventions within the HIV positive population and health promotion campaigns aimed at marginalised groups such as migrants to promote voluntary counselling and testing. The NHS should continue to provide treatment and care free to all individuals with HIV in an attempt to reduce the spread of infection, improve life expectancy and prevent the need to provide costly critical care and end of life treatment. Furthermore, additional education and training may need to take place in order for medical staff to consider HIV as a possibility sooner rather than later when they are faced with a critical case. There is also a need for the promotion of voluntary counselling and testing on a wider basis to try to encourage hard to reach groups to come forward for testing. It is also important to ensure targeted interventions aimed, for example, at men, are carried out to raise awareness of the risks of HIV transmission. Men are notoriously difficult to encourage into screening and other health service care. They do not benefit from the childbearing and reproductive health care, which regularly brings women into contact with health services. Furthermore, nationally men make up the majority of late diagnoses as well as the largest proportion of the undiagnosed HIV population in the United Kingdom²⁴; they also live with HIV for the longest period of time and therefore have a greater possibility of transmitting the infection to others.

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